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Evaluation of clinical findings and treatment options of Sydenham chorea patients

Sevgi Yimenicioğlu [1], Pelin Kösger [2]

[1] Health Ministry, Eskişehir State Hospital, Pediatric Neurology Department, Eskisehir, Turkey
[2] Pediatric Cardiologist. Department of Pediatric Cardiology, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Turkey

ORCID ID of the author(s)
SY: 0000-0002-1598-4423
PK: 0000-0002-3926-9002

Corresponding Author
Sevgi Yimenicioğlu
Health Ministry, Eskişehir State Hospital, Pediatric Neurology Department, Eskisehir, Turkey
E-mail: sevgifahri@yahoo.com

Ethics Committee Approval
The study was approved by Eskisehir Osmangazi University of Local Ethics Committee (Date: 07/01/2020, Decision no: 2020/27).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Sydenham chorea is an autoimmune neurological disorder of the childhood which occurs due to cross-reaction of antibodies against group A beta-hemolytic streptococci in the basal ganglia. We evaluated patients with Sydenham's chorea, treatment options, recovery duration, and relapses to determine whether there is any relationship between biochemical parameters such as erythrocyte sedimentation rate (ESR), serum Anti Streptolysin Antibody (ASA), and patients' clinical course.
Methods: This case series includes patients with Sydenham chorea who visited the pediatric neurology outpatient clinics between May 2013 and September 2018. Neurologic examination was performed by a pediatric neurologist, and electrocardiography and echocardiography were performed by a pediatric cardiologist. ESR and ASA levels, treatment options, and clinical course of the disease were evaluated.
Results: Sixteen patients, with nine females (56.3%) and seven males (43.7%) were included in this study. The most seen chorea type was hemichorea. The median ASA and ESR values of the patients were 619 IU/ml (278.25-794.75) and 17.5 mm/h (7.25-27), respectively. Their median age and time until recurrence were 12 (9-14.25) years and 16 months (9-18), respectively. The median recovery period was 5.5 months (3-6). Diazepam and haloperidol were the most used secondary treatment options. Mitral insufficiency (MI) was the most frequent finding (56.3%). Benzathine penicillin and secondary prophylaxis, e.g., haloperidol, diazepam were our treatment agents of choice. ASA levels were lower among patients treated with steroids (U=9, z=-2.38, P=0.017). Age was moderately positively correlated with recovery period (age r (14) = 0.738, P=0.001), while no correlation was found between age and ESR, or recurrence period (P=0.98, P=0.33, respectively). The recovery period of generalized chorea was longer than that of hemichorea (U=10.5, z=-1.96, P=0.05). Recurrence was not related to ASA levels, ESR levels, age, or recovery period (P=0.73, P=0.89, P=0.78, P=0.83 respectively).
Conclusion: High ASA levels may not indicate steroid need, and the recovery period increases with age and in cases of generalized chorea. Instead of benzathine penicillin or other known secondary prophylactic agents, azithromycin and levetiracetam can be used in hypersensitive patients.

Keywords: Sydenham chorea, Treatment, Levetiracetam, Azithromycin

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Introduction

Sydenham chorea is a central nervous system disease characterized by sudden, involuntary, non-rhythmic aimless movement, and rapid movements involving the extremities and the face. Choreiform movements disappear during sleep and rest [1, 2]. Sydenham chorea is the most common cause of acquired chorea in children and the most prominent and late finding of acute rheumatic fever [3]. It occurs because of the cross-reaction of antibodies against group A beta-hemolytic streptococci in the basal ganglia. It often presents between the ages of 5-15 years [3].

In addition to benzathine penicillin, drugs that inhibit dopaminergic hyperactivity, such as haloperidol, pimozide, and risperidone, and drugs that act on GABA, such as benzodiazepine and valproic acid are used for treatment [3]. Immunomodulatory therapies such as corticosteroids, intravenous immunoglobulins (IVIG), and plasma exchange shorten the course of the disease and reduce complications [4]. In this case series, we retrospectively evaluated patients with Sydenham's chorea, treatment options, recovery duration, and relapses, and aimed to determine whether there is a relationship between biochemical parameters such as erythrocyte sedimentation rate (ESR), serum Anti Streptolysin Antibody (ASA) and patients' clinical courses.

Materials and methods

Sixteen patients who had visited the pediatric neurology and cardiology outpatient clinics between May 2013 and September 2018 with the diagnosis of Sydenham chorea were included in this study. Patients were evaluated retrospectively. Diagnosis of acute rheumatic fever was made according to the updated Jones criteria [5].

All patients underwent detailed physical and neurological examinations. Patients' demographic characteristics, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) values, serum Anti Streptolysin Antibody (ASA), cerebral magnetic resonance imaging (MRI) reports were evaluated. ASA titers >200 IU/ml, ESH >20 mm/h, CRP >5 mg/dl were considered above the normal range.

Cardiovascular system evaluations including physical examination, electrocardiography, and echocardiography were performed by a pediatric cardiologist. Examination findings, chorea type, treatments, chorea recovery time, indications for immunomodulatory treatment, resistance to treatment, and follow-up data were retrospectively investigated. Chorea was classified into hemichorea (involving one part of the body) and generalized chorea (involving all body parts). The patients were called for a monthly check-up every 15 days until chorea improved. Symptomatic treatment of the patients continued for 2-4 months after recovery. When the symptomatic treatment was discontinued, patients were called for monthly control visits, and then at three- and six-month intervals. Cardiac controls were planned according to the severity of heart involvement.

Statistical analysis

Statistical analyses were performed using SPSS 15.0 (SPSS for Windows, Version 15.0. Chicago, SPSS Inc.) program. Normally distributed variables were presented as mean (standard deviation), and non-normally distributed variables were presented as median (minimum-maximum). In the comparison between the independent groups, t-test was used for the parametric data and Mann-Whitney U test was used for the non-parametric data. The difference between the categorical data was evaluated by Chi-square and Fisher's exact tests. *P*-value <0.05 was considered statistically significant.

Results

A total of 16 patients, comprising 9 females (56.3%) and 7 males (43.7%), were included in this study. The median age of the patients was 12 (9-14.25) years. The demographic features are summarized in Table 1. The highest, lowest, and median ASA levels were 1330 U/ml, 96 U/ml, and 619 (278.25-794.75) U/ml. The patient who had an ESR of 39 mm/h also had elevated CRP (6.2 mg /dl). The CRP values of the rest of the patients were within normal limits. Echocardiography of the same patient showed mild mitral valve insufficiency compatible with carditis.

Table 1: Demographic features

Features	
Total	16
Gender	Female 9(56.3%)
	Male 7 (43.8%)
Median Age	12(9-14.25)
ASA	619(278.25-27)
ESR	17.5(7.25-27)
Chorea	Hemichorea 68.8%
	Generalized 31.2%
Cardiac involvement	12 patients 75%
	MI 56.3 %
First Treatment Choice	Diazepam+Haloperidol 56.3%
Recovery period	5.5 months (3-6)
Recurrence	3 patients (18.8%)

Chorea was generalized in 5 (31.2%) of patients and presented as hemichorea in 11 patients (68.8%). At the time of admission, 4 (25%) patients had right hemichorea, 7 (43.8%) patients had left hemichorea, and 1 patient had generalized chorea. Four patients with hemichorea developed generalized chorea later. Recurrence was seen in 2 of 3 generalized chorea patients. All clinical characteristics are presented in Table 2.

Table 2: Clinical characteristics of the patients

Patient	Gender	Age	ASA	ESR	Recovery time Months	Relapse Months	Chorea	Drugs used	Steroid	Heart involvement
1	F	12	303	28	6	-	Right, then Generalized	Diazepam, Valproic acid	+	MI
2	F	15	870	27	6	16	Left	Haloperidol ,Diazepam	-	MI
3	F	9	606	18	6	-	Generalized	Haloperidol,	+	MI
4	F	9	382	6	4	-	Left	Haloperidol, Diazepam	-	MI
5	F	15	111	15	9	-	Right then Generalized	Valproic acid then Haloperidol, Diazepam	+	MI,AV Block
6	M	9	1330	4	2	-	Right	Haloperidol, Diazepam	-	2^0MI
7	M	10	797	11	5	-	Left	Haloperidol, Diazepam	-	2^0MI
8	F	12	632	6	6	-	Right	Haloperidol	-	Normal
9	M	15	360	27	10	-	Left then Generalized	Haloperidol, Diazepam,	+	Normal
10	M	15	683	15	7	-	Left	Haloperidol,	-	MI,TI
11	F	12	738	39	4	-	Left then Generalized	Haloperidol	+	Acute Carditis
12	F	12	237	38	3	-	Left	Haloperidol, Diazepam	-	Normal
13	M	11	96	5	6	18	Left	Levetiracetam.	+	MI
14	M	7	788	20	2	9	Right	Haloperidol, Diazepam	-	Normal
15	F	6	>800	25	2	-	Left	Haloperidol, Diazepam	-	2^0 MI
16	M	12	270	17	3	-	Right	Haloperidol, Diazepam	+	MI

AV: Atrioventricular Block, MI: Mitral insufficiency, TI: Tricuspid Insufficiency

All generalized chorea patients and 2 (18.2%) of the hemichorea patients were treated with methylprednisolone. Five patients with generalized chorea findings were admitted to the hospital and administered 1 g daily methylprednisolone for three days, followed by oral prednisolone tapered within one month. Three patients had recurrence. Methylprednisolone was not

considered in one of these patients with recurrence, whose findings responded to haloperidol. In one of the 2 patients with recurrent generalized chorea, complaints were observed 16 months after the end of the treatment. The third patient with recurrence had a history of anaphylaxis to benzathine penicillin G. Allergic rash developed with erythromycin and clarithromycin, and chorea symptoms could not be controlled with haloperidol or valproic acid. This patient was admitted to the pediatric neurology clinic due to increased involuntary movements and difficulty in self-care skills 18 months after recovery. Recurrence findings were consistent with generalized chorea and levetiracetam was administered. Because of the history of anaphylaxis to benzathine penicillin, azithromycin 500 mg tablets were used for secondary prophylaxis every 10 days.

In all patients, first haloperidol, a dopamine receptor antagonist, then diazepam, a benzodiazepine, were used to control movement disorders. The combination of diazepam and haloperidol was used in 9 patients (56.3%), only haloperidol was used in 4 patients (25%), diazepam and valproic acid combination were used in 1 patient (6.3%), diazepam, valproic acid and haloperidol combination were used in 1 patient (6.3%), and levetiracetam was administered to 1 patient (6.3%). Clinical recovery was the marker for the duration of chorea treatment. The recovery period of generalized chorea was longer than that of hemichorea (U=10.5, z=-1.96, *P*=0.05). Drugs were discontinued within 2 months after symptoms were controlled. Benzathine G penicillin was used for secondary prophylaxis. The median recovery period was 5.5 months (3-6). Recurrence of the chorea was seen in 3 (18.8%) patients, two (12.5%) of which were males. ASA was high in two and ESR was above 20 mm/h in one patient with recurrence.

Upon cardiac examination, 12 patients (75%) were found to have carditis. One of them was prescribed aspirin because of acute rheumatic carditis signs. Four patients had isolated chorea without heart involvement. Compared to males, insignificantly more females had cardiac involvement (*P*=0.77). MI was the most frequent finding in chorea (56.3%). Elevated ESR and cardiac involvement were not correlated (*P*=0.52). Brain MRI was performed in all patients and yielded normal results in all. There was a moderate positive correlation between age and recovery period (age r(14)=0.738, *P*=0.001)), while age, ESR, and recurrence period (*P*=0.98, *P*=0.33 respectively) were not correlated. Recurrence was not related to ASA levels, ESR levels, age, or recovery period (*P*=0.73, *P*=0.89, *P*=0.78, *P*=0.83 respectively.

Discussion

Sydenham chorea can be seen alone or in combination with other symptoms of acute rheumatic fever. While it usually starts unilaterally, bilateral choreiform movements may also be observed. It mostly presents as generalized chorea, and less often as hemichorea. The handwriting of the patients is impaired because they cannot perform tasks requiring fine motor skills due to choreiform movements in the hands. Speech impairment may be observed [2, 6, 7]. Motor motion instability is particularly noticeable during protrusion of the tongue and ocular fixation. Sydenham chorea is included in the major criteria for acute rheumatic fever according to the 1992 modified Jones criteria and sufficient for diagnosis [8]. Among all our patients, one presented with generalized chorea. Generalized chorea developed later during the disease in four patients who presented with hemichorea. This was attributed to incompliance with symptomatic treatment. Although very rare, the patient may become bedridden (chorea paralytic). Sydenham chorea is observed in 40-80% of patients with carditis, and 10-30% with arthritis. In 20-70%, it is the only symptom [9]. In our study, only one patient had acute carditis, and 12 patients had carditis compatible with rheumatic heart disease. The findings were consistent with isolated chorea in four patients. None of the patients had arthritis at the time of diagnosis.

Sydenham chorea and acute rheumatic fever are seen at similar ages, between 5-15 years, often around 9 years of age, and mostly in females [3, 6, 7]. In this study, the median age of chorea patients was 12 years (9-14.25) and most were females (56.3%). The youngest patient was a 6-year-old female.

It occurs 1 to 6 months after tonsillopharyngitis / pharyngitis caused by GABHS. Our patients did not have any upper respiratory tract infection at the time of diagnosis. One 6-year-old female patient had had an upper respiratory infection twice in the last 6 months. A 12-year-old female who presented with an acute carditis attack had received benzathine penicillin G treatment for tonsillitis and was diagnosed with chorea and acute carditis 1 month later.

Chorea symptoms mostly last between 8-15 weeks, while they can continue anywhere from 1 week to 2 years. Relapse may be observed in completely healed patients for up to 2 years [2, 6, 7]. The median recovery time of our patients was 5.5 months, and the latest improvement was observed 10 months later. Three (18.8%) patients had relapsed at 9 months, 16 months, and 18 months, respectively, after treatment. The patient presenting with relapse 9 months after the initial diagnosis had discontinued haloperidol 3 months before recurrence symptoms. He presented with hemichorea on the same side. The patient was started on haloperidol again and symptoms were controlled.

SC is the result of secondary immune reactivity against the basal ganglia and the brain [1, 2, 6, 10]. Antibody-related D2R signals, especially in dopaminergic neurons, lead to changes in central dopamine pathways and impaired movement [10].

While the amounts of GABA and acetylcholine in the basal ganglia are reduced, dopaminergic activity is increased, which also explains the mechanisms of action of haloperidol, valproic acid, and carbamazepine [2, 11]. Therefore, antiepileptics (valproic acid, carbamazepine) or dopamine receptor blockers (haloperidol, pimozide, risperidone) may be used in the symptomatic treatment of chorea [12, 13]. In this article, dopamine receptor antagonists were used as the first choice, and benzodiazepine was used as an add-on treatment to haloperidol to control movement disorders. Levetiracetam was started in one of the patients who did not benefit from haloperidol and valproic acid treatment. Although the mechanism of action of levetiracetam is not fully known, it has little affinity to GABA and glutamate receptors and is effective in preventing negative modulation against GABA receptors without direct binding [14]. In light of this information, it may be said that levetiracetam could lead to an increase in the efficacy of GABA. Levetiracetam reduces the synchronization of neurons in epilepsy patients and has been reported to improve movement disturbance in some movement

disorders such as essential tremor, cerebellar tremor, myoclonus, and dyskinesias caused by L-dopa [15]. Vlas et al. [16] used levetiracetam to successfully control choreoathetosis in two patients with dyskinetic CP. Şahin S et al. [17] used haloperidol in a patient diagnosed with chorea and added levetiracetam when it was ineffective, after which improvement was observed.

Because Sydenham chorea is an immune-mediated disease, corticosteroids, intravenous immunoglobulin, and plasmapheresis were shown to have benefits in selected cases. They shorten the disease course and reduce complications [9,18,19,20]. Immunosuppressive therapy is used in severe, resistant cases, in patients with side effects to symptomatic therapy, or in those who do not respond to symptomatic therapy [21]. Among our cases, methylprednisolone treatment was started in 7 (43.8%) patients. All but one of the patients receiving methylprednisolone had high ASA titers, and 3 had high ESR values.

The primary treatment of Sydenham chorea is penicillin and bed rest [22]. Penicillin prophylaxis is given for cardiac protection and does not affect relapse [2]. Azithromycin may be used in the acute period of streptococcal infections, and in some studies, the superiority of amoxicillin-clavulanate has been reported [23], although it is not recommended for secondary prophylaxis in acute rheumatic carditis [24]. We used azithromycin for secondary prophylaxis in our patient who developed a severe allergic reaction to benzathine penicillin G and an allergic rash because of erythromycin and clarithromycin. Azithromycin was used every ten days a month. No recurrence of streptococcal infection was observed with azithromycin prophylaxis. There was no deterioration in rheumatic heart disease in cardiologic controls.

Sydenham chorea symptoms improve by 6 months in most patients. Three of our patients had recurrence, one of which was female. She did not use the penicillin prophylaxis properly. The other patient had an allergic reaction to benzathine penicillin, erythromycin, and clarithromycin, and had insufficient secondary prophylaxis. Both patients with recurrence were noncompliant with secondary prophylaxis. One of these patients had a high ASA value. Recurrences most commonly occur in 1-2 years after the onset of the disease. Recurrence is defined as a new finding of chorea that lasts for at least 24 hours, occurring at least 2 months after the first attack. Recurrence is related to incompliance with prophylactic treatment, re-exposure to streptococcal infection, and no remission within the first 6 months [3, 25]. Regular penicillin prophylaxis reduces the risk of recurrence [14].

None of the patients had persistent chorea, which is characterized by symptoms lasting for more than a year [26, 27]. In the study of Gürkaş et al. [25], there were four persistent chorea patients, among which 3 had recurrence. In these patients, valproic acid was added when haloperidol was ineffective in secondary prophylaxis. According to Tumas et al. [26], persistent chorea occurs because of the molecular changes caused by haloperidol in the basal ganglia.

Treatment strategies in SC are mostly based on the physician's clinical decision-making. According to Dean and Singer, data on symptomatic therapy are based on case report presentations; therefore, individually made decisions by the practitioner are important [19].

Limitations

The limitations of this study include its retrospective and single-center design, and few numbers of patients. Instead of case reports, further studies may be planned to figure out the treatment strategies and risk factors for recurrent and persistent Sydenham's chorea.

Conclusions

Sydenham Chorea is one of the major signs of acute rheumatic fever. There is a risk of recurrence in patients using insufficient secondary prophylaxis. It may become generalized in patients presenting with hemichorea and not receiving adequate symptomatic treatment. Reaction to antiepileptics and dopamine antagonist drugs is extremely rare and makes it difficult to control symptoms. In these cases, levetiracetam may be a useful choice. Despite advances in medicine, Sydenham chorea treatment is not evidence-based. Treatment should be tailored to the clinical findings of each patient.

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