

R E V I E W

Therapeutic aspects of Sydenham's Chorea: an update

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Abstract. Sydenham's Chorea (SC) is a hyperkinetic movement disorder associated with neuropsychiatric manifestations. It is believed to be caused by the autoimmune response following a group A beta-hemolytic streptococcal (GABHS) pharyngitis, and it is one of the major diagnostic criteria for Acute Rheumatic Fever (ARF) diagnosis. Despite having been known and studied for centuries, there are still no standardized therapies or official guidelines for SC treatment, so that it is necessarily left to physicians' clinical experience. Antibiotic treatment, symptomatic therapies, and immunomodulatory treatment are the three pillars upon which SC patients' management is currently based, but they still lack a solid scientific basis. The aim of this writing is precisely to review the state of the art of SC's treatment, with an overview of the advances made in the last 5 years. However, since the therapeutic uncertainties are a mere reflection of the severe gap of knowledge that concerns SC's pathogenesis and manifestations, the importance of high-quality research studies based on homogenized methodologies, instruments, and measured outcomes will also be stressed. (www.actabiomedica.it)

Keywords: Acute Rheumatic Fever, Beta-Hemolytic Streptococcal Pharyngitis, Hyperkinetic Movement Disorder, Sydenham's Chorea

Background

Sydenham's Chorea (SC) is a hyperkinetic movement disorder associated with neuropsychiatric manifestations.

Choreic diseases are widely known since the Middle Ages when their typical involuntary, irregular, semi-directed, dance-like (*χορεία* means "dance" in Ancient Greek) movements were given mystical and religious explanations (hence the antique name of "Saint Vitus' Dance"), but it was only in 1686 that Thomas Sydenham firstly distinguished a particular subgroup among these diseases, writing about "a kind of convulsion, which attacks boys and girls from the tenth year to the time of puberty"(1).

Over the years, countless epidemiological studies proved him right, demonstrating that SC's prevalent

age of onset is 5-15 years, with a peak at 8-9 years (2), but also provided us with much more information: SC is the most common form of acute acquired chorea in children (3, 4); it is generally bilateral, but about 20% of patients present hemichorea; in most case series there is a female preponderance; it takes 4-8 weeks after the emergence of pharyngitis for SC to appear. On the other hand, further research will be needed to clarify the differences found by different authors in the average duration of the choreic symptoms, which ranges from a few weeks (5) to 2 years (6), but it is now widely accepted that SC's believed self-resolving nature is overshadowed by possible persistence of symptoms and not rare recurrences (7).

Thomas Sydenham also wrote about another disease, today is known as Acute Rheumatic Fever (ARF), but he could not associate it with SC. It took many

centuries of further investigations to understand the epidemiological and pathogenic connections between SC and ARF, which over time became so strong led to the inclusion of SC among the major Jones criteria for ARF's diagnosis (8).

ARF is an inflammatory postinfectious disease. It is a sequela of the autoimmune response following pharyngitis caused by *Streptococcus Pyogenes*, also known as "Group A β hemolytic Streptococcus (GABHS)". It is believed to be caused by molecular mimicry, the main mechanism by which infectious pathogens can cause autoimmunity: following frequent expositions to GABHS, predisposed individuals develop autoreactive lymphocytes and antibodies directed against GABHS epitopes which cross-react with human cells (9). This autoimmune pathogenesis explains the heterogeneity of ARF's manifestations, which typically are skin involvement, joint pain, fever, cardiac involvement (i.e. Rheumatic Heart Disease, which causes about 233.000 deaths each year, with a prevalence of about 15 million people worldwide and an incidence of 282.000 new cases) (10), and SC. In particular, SC is believed to be caused by autoantibodies directed against basal ganglia epitopes (11). A pivotal study published in 1997 by Cardoso et al. stated that SC affects about one-quarter of ARF patients (12), but more recent studies have questioned this data, talking about one-third or 10-15% (10, 13). This variability may depend on regional variations in ARF's manifestations, because SC may be a more or less frequent ARF's manifestation in different world regions, but also in ARF's diagnosis: in developing countries, SC easily leads to ARF diagnosis, but other ARF's manifestations may not be so easily recognized, increasing the percentage of SC cases reported in ARF patients.

However, it would be reductive to simply consider SC a condition affecting a minority of ARF patients, not only because persistence and recurrences can prolong it, but also because chorea can be associated with so many neurological and neuropsychiatric manifestations that it would be more correct naming it "Sydenham's Disease" (5). The most common accompanying neurological symptoms are tics, hypometric saccades, oculogyric crises, dysarthria, reduction of verbal fluency, dysexecutive syndrome, migraine, and muscular hypotonia (until the so-called "chorea paralytica", a

severe decrease in muscle tone observed in 1,5% of cases) (2). As concerns the neuropsychiatric manifestations, there are several case reports showing that obsessive-compulsive disorder, anxiety, mood disorders, psychotic features, tics, ADHD, and several aspecific symptoms, such as emotional lability, irritability, and regressive behavior, are particularly common in SC patients (3). Although these neuropsychiatric manifestations have been known since 1960(14), their exact prevalence is still debated and the timing of symptom onset is still not clear.

Despite the great advances in research and in therapeutic improvement in many neurological fields, the most severe gaps in our knowledge of SC concern its treatment (15-21). At the time of this writing, there are no approved guidelines for SC and, even though many effective drugs are known, almost none of them is supported by good quality research, so that clinicians' therapeutic choices are often mainly guided by their clinical experience. Available treatments can be divided into three key groups: antibiotic therapy, symptomatic therapy, and immunomodulatory therapy. Among them, antibiotic prophylaxis is the only one to be well defined, since it does not only concern SC, but it is used in all ARF patients: benzathine penicillin G administered orally or IM for both primary and secondary prevention(22). On the other hand, the latter two categories count numerous pharmacologic treatments in use for several pediatric and other diseases, many of which are only supported by small, non-controlled case reports (23-27). Dopamine antagonists (also known as "neuroleptics") and antiepileptic drugs are the two cornerstones of symptomatic treatments. Antidopaminergic agents' rationale lies in the fact that SC is believed to be caused by the autoimmune alteration of the basal ganglia circuitry (11). Haloperidol and Pimozide seem to be the most promising ones, but extrapyramidal side effects were reported (13). For this reason, the usage of antiepileptic medications, such as Valproic acid and Carbamazepine, is often preferred. Since SC is believed to be an autoimmune disease, usage of immunomodulatory treatments has often experimented with. Because of their well-known systemic side effects, steroids are generally restricted to severe cases, but their usage is supported by well-reported effectiveness. Other immunomodulatory treatments,

such as IVIG and plasmapheresis also look promising, but there are only a few publications about them, and further studies will be needed to prove their efficacy and safety in SC patients(28-30).

Figure 1 represents the treatment Algorithm for Sydenham's Chorea (Figure 1).

Symptomatic Treatment

Concerning the symptomatic treatment of Sydenham Chorea (SC), due to limited scientific evidence, based only on case reports, case series, small comparative series, and a single randomized placebo-controlled, treatment decisions depend on the physician's

clinical experience (31). There are limited studies of symptomatic treatment of SC in adults and even fewer studies of childhood treatment. To date, at our knowledge, there are no reported randomized, placebo-controlled trials of symptomatic treatment of SC in childhood (32, 33). Symptomatic treatment of the illness has not been well-studied. Case reports, case series, expert opinions, and small comparative studies, and uncontrolled comparison studies have supported the use of dopamine antagonists (i.e. antipsychotics) and anticonvulsants in the treatment of SC related chorea, leading to faster symptom resolution and functional improvement. Treatment of the acute symptomatology of SC is directed at minimizing symptom severity and shortening the course of illness.

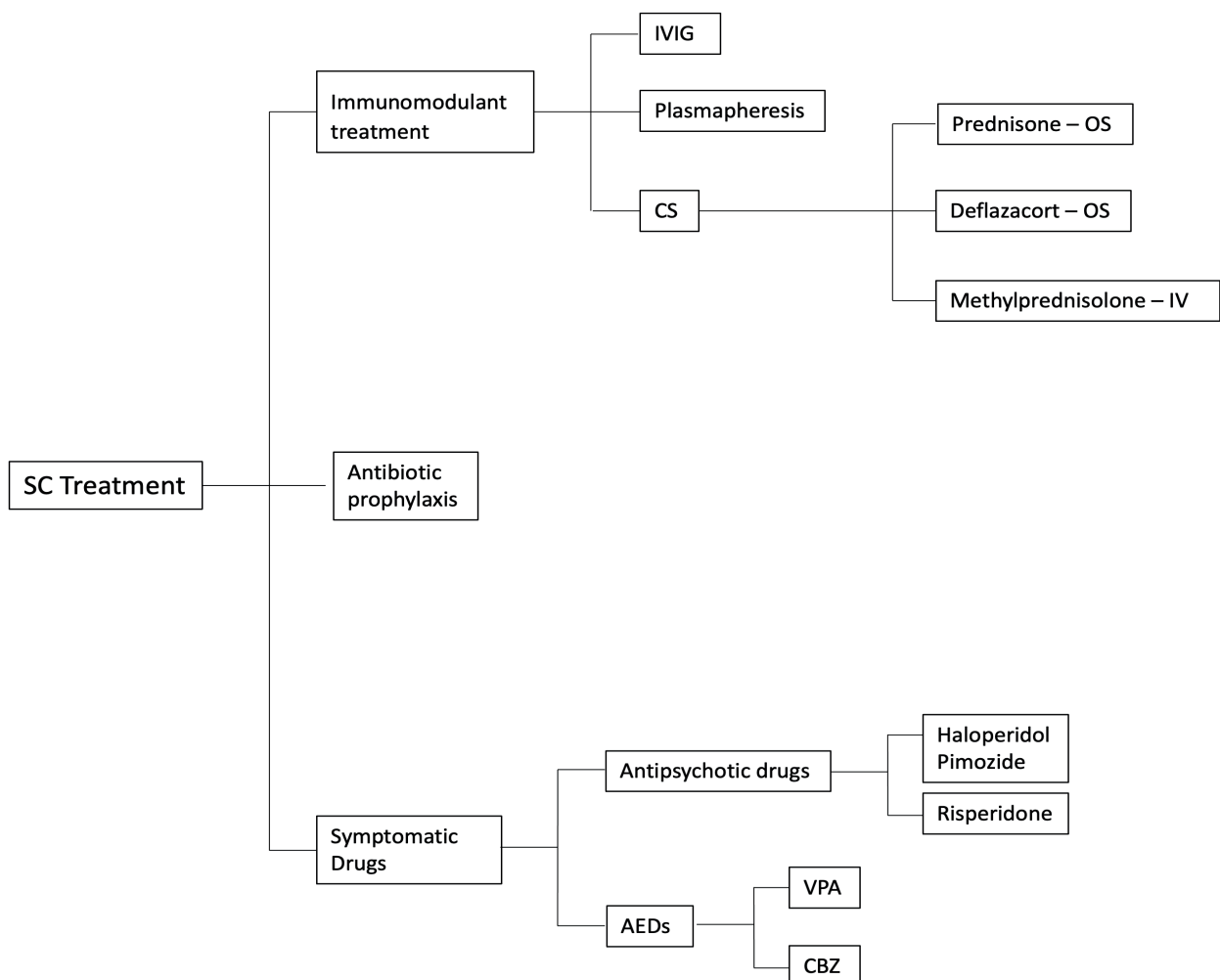


Figure 1. Treatment Algorithm for Sydenham's Chorea

The abnormal movements may be the result of excessive dopaminergic neurotransmission and a deficit of cholinergic and gamma-aminobutyric acid neurotransmission in the basal ganglia.

Several studies demonstrated the efficacy of the use of a low-dose high-potency dopamine 2 (D2) receptor blocking agent (eg, haloperidol [0.01-0.02 mg/kg/day orally twice a day to thrice a day], fluphenazine, pimozide). Haloperidol provided a significantly faster improvement in chorea, reducing frequency and amplitude of the choreoathetoid movements, but was associated with more withdrawals due to side effects, compared with pimozide. A potential complication of this therapy is an acute drug-induced movement disorder such as akathisia or dystonia (34). If this develops, anticholinergic treatment with benztropine or diphenhydramine followed by withdrawal or reduction of the D2 blocking agent is appropriate. Therefore, haloperidol should be reserved for severe cases and used with caution. Shannon and Fenichel (35) have suggested that pimozide may have fewer neuropsychiatric side effects than haloperidol but has a higher risk for cardiac side effects of arrhythmia and prolongation of the QTc interval. They have also suggested that pimozide has virtually no effect on nor-epinephrine receptors, and so low doses (2 mg, twice a day) and short-term treatment have a lower risk for the appearance of tardive dyskinesia while improving SC symptoms. It could be useful in extreme situations such as chorea paralytica. In milder cases of SC, or when clinicians or families are reluctant to try D2 blocking agents, other reasonable alternatives include - Valproic acid (20-25 mg/kg/day), which is one of the first-line therapeutic options for the treatment of chorea in childhood. It stimulates gamma-aminobutyric acid activity, effectively suppressing the motor signs. However, its long-term side effects on bone metabolism increase the risk of polycystic ovary syndrome, and teratogenic effects should be kept in mind in children and adolescents, particularly the ones who may require longer treatment duration. - Carbamazepine (15 mg/kg/day) increases the acetylcholine level in the striatum inducing a new equilibrium in the balance of the dopaminergic and cholinergic systems.

Most treatment studies involve small series of patients treated open-label, making it difficult to distinguish the benefit of medication from the expected spontaneous improvement over time.

Agents that have been reported to be effective in SC include Haloperidol (36-38), Carbamazepine (39), Valproic acid (40), Phenobarbital (38), Diazepam (38), Chlorpromazine (38). Currently available options for treating childhood CS are many but often result in less-than-complete benefits. A large number of etiologies, the complex pathophysiology, and the presence of off-target effects for most available medications contribute to the therapeutic challenges. With a rational and systematic approach, prioritizing treatment of chorea that causes disability, the meaningful clinical benefit can often be achieved(32).

Immunomodulant Treatment

SC is an autoimmune disorder, so immunomodulatory treatment has also been used in severe and refractory cases and in patients developing severe side effects on symptomatic therapy (41, 42) to shorten the course of the illness and prevent complications (43, 44)

Corticosteroids

Oral prednisone, oral deflazacort, and intravenous (IV) methylprednisolone are the immunomodulatory drugs most studied in SC, with all having a high rate of improvement (31).

In an observational study by *Fusco et al.*, 10 patients with a paralytic form of SC were treated with IV methylprednisolone for 5 days (25 mg/kg per day), followed by oral therapy with deflazacort for 3 months (0.9 mg/kg/per day). After starting IV methylprednisolone, the deglutition improved in the first 48 h in all children, and in the first seven days, all patients recovered the ability to walk unassisted(45). Other studies (31, 41, 43)confirm the efficacy of using a pulse therapy with IV methylprednisolone for 5 days (25mg/kg per day) followed by oral prednisone (1 mg/kg/die) or deflazacort (0.9 mg/kg/die) to treat refractory symptoms or in the acute stage. In these studies, steroids represent either initial treatment or treatment following a previous therapy failed.

In a randomized observed double-blinded study by *A.Paz et al.*, 22 patients with severe SC were treated with prednisone (2 mg/kg/die, maximum dose 60 mg/

die) and the other 15 patients with placebo(46). In another retrospective study of *Tumas et al.*, five patients were treated with oral prednisone (1 mg/kg) for 15 days after haloperidol failed to control the abnormal movements(13). The results of these studies indicate that adjunctive treatment with prednisone reduced the intensity and duration of acute SC. However, there are some limitations of these studies, for example, the use of a non-validated rating scale for SC or the develop-

ment of side effects that have compromised the double-blinded study by *A.Paz et al.* Only one failure of steroid treatment was reported(29, 43).

In our opinion, reviewing most of all available literature, the use of IV or Oral steroids was always successful (13, 29, 41, 45-53).

Table 1 summarizes the principal studies about corticosteroids for acute Sydenham's Chorea (Table 1).

Table 1: Principal studies about using of corticosteroids for acute Sydenham's Chorea

Authors	Study Design	N and Age of patients treated	Drugs and Dose	Chorea Duration	Outcome	Adverse reactions
Fusco C. et all (45)	Observational	N: 10 Age: 7-11	Methylprednisolone IV: 25 mg/kg/die for 5 days - Deflazacort OS: 0,9 mg/kg/die for 1 month	10-15 days	Response in 21 days	None
Cardoso F. et all (41)	Observational	N: 5 Age: 11-46	Methylprednisolone IV: 25 mg/kg/die for 5 days - Prednisone OS: 1 mg/kg/die	5 years	Response in 5 days	Cushing syndrome.
Paz JA. et all (46)	Randomized double-blinded	N: 22 Age: 7-13	Prednisone OS: 2 mg/kg/die for 4 weeks follow by gradual discontinuation	2-90 days	Response in 1 week	None
Tumas V. et all(13)	Retrospective	N: 5 Age: 2-36	Prednisone OS: 1 mg/kg/die for 15 days follow by gradual discontinuation	4 d – 8y	Response	None
Miranda M. et all (29)	Case Report	N: 1 Age: 16	Methylprednisolone IV: 1g/kg/die for 3 days - Prednisone OS: 1 mg/kg/die	3 days	No response	None
Faustino PC. et all (47)	Observational	N: 19 Age:9-15	Prednisone OS	Not defined	Response	None
Fusco C. et all (44)	Case series	N: 5 Age: not defined	Methylprednisolone IV: 25 mg/kg/die for 5 days - Deflazacort OS: 0,9 mg/kg/die for 3 months	Not defined	Response in 45 days	None
Barash J. et all (49)	Case report	N: 5 Age: 2-30	Prednisone OS: 2 mg/kg/die for 3 weeks	5 – 30 days	Response in 7-12 days	None
Garvey MA. et all (52)	Randomized	N: 6 Age: 7-13	Prednisone OS: 1 mg/kg/die for 10 days	7-19 weeks	Response in 1 month	Weight gain
Teixeira AL. et all (53)	Case report	N: 4 Age: 4-12	Methylprednisolone IV: 25 mg/kg/die for 5 days - Prednisone OS: 1 mg/kg/die follow by gradual discontinuation	6-8 weeks	Response in 1 month	Moon facies and weight gain
Araujo A. et all (51)	Observational	N: 14 Age: 6-12	Prednisone OS	4-8 months	Response in 6 d – 22 m	None

IVIG

Another treatment option for chorea is IVIG, as neuronal antibodies are involved in the pathogenesis of SC(54). A low-quality cohort study by *Zykov et al.* of patients with tic disorders (n=60), of whom seven with caudate nucleus antibodies were treated with IVIG, showed a reduction in the average number of tics immediately after IVIG compared with baseline (15.3 vs 21.6, $p=0.05$). A non-significant reduction was found at 6 months follow-up (55, 56). In a double case report by *Van, Immerzeel* patients were treated with IVIG (400 mg/kg for 5 days) as second-line therapy. Treatment was well tolerated and had a pronounced positive effect on clinical symptoms (57). In two other cases, authors report that the utilization of IVIG over 5 days got improvements in patients (58, 59). Using IVIG for second or third-line therapy, other authors reported an improving of acute SC's symptoms and a better outcome (28, 60). However, as well as for corticosteroids studies, in IVIG studies there are the same limitations.

In summary, all patients appeared to respond to IVIG, including an additional comparison study of IVIG, plasmapheresis, and steroids (discussed below). No reports of clear IVIG failure have been published at our knowledge and no publications described particularly side effects concerning the use in SC (43).

Plasmapheresis

The third option after failure of conventional drugs and IV corticosteroids is plasmapheresis (29). Although their biological role has not been unequivocally demonstrated, anti-basal ganglia antibodies (ABGA) have been found in 100% of patients with acute SC (61) and their presence provides a rationale for the use of plasmapheresis (45, 62). In a case report by *Miranda et al.* a six-year-old girl with acute SC was treated with five rounds of plasmapheresis with a rapid improvement of hypotonia (29). In a randomized, controlled study by *Garvey MA*. 18 children with SC received plasmapheresis, IVIG, or prednisone. 8 patients were treated or with plasmapheresis as second-line therapy after symptomatic drugs (n=5) or with plasmapheresis alone (n=3). 6 patients had clinically significant remission of symptoms by the 1-month fol-

low-up (52). Although this improvement was not significant, the study may not have been adequately powered to detect a meaningful difference in plasmapheresis, IVIG, or prednisone between the treatment group(62). No side effects were reported in published studies(43). In summary, there are few studies about the use of plasmapheresis in acute SC and there are the same limitations found corticosteroids and IVIG studies so, in our opinion there is insufficient evidence to support or refute the use of plasmapheresis in the treatment of SC (62).

Expert Opinion

SC is a debilitating pathology, who deserves to be known by pediatricians and neurologists.

SC treatment is based on three milestones: antibiotic prophylaxis, to eradicate Group A Beta-Hemolytic *Streptococcus*' infection; immunomodulatory treatment, with corticosteroids, immunoglobulins, or plasmapheresis, given the autoimmune nature of this disorder; symptomatic drugs, to improve patient's clinical conditions. Antiepileptic drugs, such as Valproic Acid and Carbamazepine, and antipsychotic drugs, such as Haloperidol, Pimozide, and Risperidone, are often used to control SC symptoms, with a very good outcome.

Concerning immunomodulatory treatment, the overall clinical experience to support the use of immunomodulatory therapies in SC is limited. Steroids have the strongest data with prospective, double-blind randomized controlled trials and prospective or retrospective case series having been reported.

The potential side effects, the overall limited scientific evidence, and the fact that SC usually resolves spontaneously or improves with symptomatic therapy has led to a tendency to reserve these alternatives for severe cases such as chorea paralytica and for resistant cases, such as those patients with disabling symptoms who fail, or cannot tolerate, symptomatic treatment.

The decision to use immunomodulatory therapies for SC should be made on an individual basis as the benefits must outweigh the risks for each patient (63). Thus, the practitioner should consider the severity of the problem, availability of a therapeutic agent, cost

to the family, extent of supporting evidence and the therapy's side effect profile.

High expression of the D8/17 marker was considered a potential candidate marker to identify patients upon presentation who would benefit from immunomodulatory intervention.

SC typically improves gradually, with symptoms typically lasting 12 to 15 weeks.

Full recovery occurs in almost all patients, but symptoms occasionally persist for two years or more. According to the literature, persistent Sydenham's chorea (PSC) may be related to the development of molecular changes in the basal ganglia induced by haloperidol treatment, however persistence has been shown also in patients treated with sodium valproate. So this hypothesis does not seem valid.

Moreover, non-immune mechanisms seem to be associated with the pathogenesis of PSC. Data suggest that the persistence of choreic involuntary movements in SC is not associated with persistent lymphocyte dysfunction. Specially, the percentages of B1 cells (a subset of B lymphocytes increased in autoimmune conditions) are not changed in remitted SC or persistent SC. Therefore patients with PSC may not be candidates for immunosuppressive or immunomodulatory therapies.

Basal ganglia structural damage may occur during the acute phase of SC, leading to persistent involuntary choreic movements and thus to PSC in a subgroup of patients. In line with this hypothesis, neuroimaging studies have demonstrated that patients whose choreic movements remitted completely did not present with lesions of the basal ganglia.

PSC could be characterized by both motor and psychiatric disorders. The frequency of psychiatric disorders did not differ between SC patients in remission in comparison with patients with persistent chorea, except for depressive disorders which were more frequent in the latter. This could be related to lower levels of BDNF (brain-derived neurotrophic factors) demonstrated in patients with PSC when compared to both controls and acute SC patients (63).

The irregular usage of antibiotic prophylaxis, failure to achieve remission within 6 months, and prolongation of symptoms for more than 1 year are risk factors for recurrence of chorea.

For the recurrence, the recurrence rate is about 15 to 30%: it has been reported as 25% in Australia and 20% in Brazil, Israel and the United States. Even though, recent investigations suggest that recurrent forms of SC are more common than previously recognized. One prospective study reported that 42% of the sample with resolved SC experienced a recurrence of symptoms anywhere from 3 months to 10 years following the initial episode. Half of these subjects were found to have evidence of GAS infections. Therefore, most relapses may be due to repeat group A streptococcal infections. Patients not receiving continuous antibiotic prophylaxis are at increased risk. In some reports recurrence was seen only in such patients. Even though, a significant number of patients showed recurrent SC symptoms without any detectable preceding infection or identified trigger.

Additional studies documenting persistent psychiatric symptoms(64), permanent basal ganglia damage(65), and impaired executive function in adulthood (66), provide further evidence that the complications of SC may remain long after the adventitious movements have resolved.

MRI studies in patients with SC have demonstrated permanent lesions of the basal ganglia secondary to SC. Emery and Vieco (65) reported abnormal signals and enlargement of the caudate and putamen in the acute period followed by evolution of this hyperintensity to a persistent cystic appearance 40 months later. Faustino et al. (47) reported that 3 patients with a permanent lesion of the basal nuclei had a prolonged duration of chorea and all presented with the recurrence of chorea. Also in another study(13) 4 patients had noticeable structural lesions in the basal ganglia, 3 had small hyperintense foci located in the caudate nucleus, and 1 had intense, bilateral, striatal hyperintensity in T2-weighted and fluid attenuation inversion recovery, hypointense T1-weighted MR images, and another lesion on the right dentate nucleus. The patient with severe striatal damage and 1 of the 3 patients with slight imaging abnormalities in the caudate nucleus had unremitting chorea for 11 and 8 years, respectively.

These findings reveal that there may be mechanisms other than the reactivation of rheumatic fever in recurrences of SC. In some patients, permanent basal

ganglia damage, which occurs during the course of the disease, may cause prolongation of symptoms and recurrences of chorea. In this case, the recurrence may be the outcome of permanent subclinical damage following the initial SC episode. Whether longer duration of symptoms causes this damage or damage causes the persistent course has not been demonstrated. In any case, what determines the propensity of a patient to develop permanent damage is still unknown, it may be related to an individual immunological response.

However, late recurrences are unlikely to have an immune pathophysiologic basis (these cases are usually anti-basal ganglia antibodies [ABGA] negative)(67). Being that the clinical course of the disease is important in the recurrence of chorea, it is hypothesized that they are more likely to be the result of a dopamine hypersensitivity in a previously damaged basal ganglia. Also, the development of a co-existent pathology such as dementia or simply cumulative neuronal loss associated with ageing may be sufficient to produce dysfunction in previously damaged basal ganglia leading to the late re-emergence of chorea.

SC also can reoccur during pregnancy (chorea gravidarum) and it can be induced by oral contraceptives(68). Repeated recurrences are less common. No clinical parameters are available to identify at initial presentation patients with higher risk of recurrence.

Recurrence should also prompt the clinician to consider other autoimmune or metabolic/mitochondrial diagnoses(69). The risk of chronic rheumatic heart disease is increased among patients with recurrent GAS infections and recurrent SC. Rheumatic recurrences can develop new valve damage evidenced by echocardiography. Also, patients with pure SC who initially had only subclinical valvulitis with echocardiography may develop evidence of valvular regurgitation. Since many previous reports have confirmed that patients with cardiac involvement are at greater risk for recurrence, the finding of subclinical valvulitis in some patients with pure SC emphasizes the need for a longer duration of secondary prophylaxis in this patient group(70, 71) (72)

The literature being studied for this review shows how important would be the creation of some guidelines, to standardize the diagnostic and therapeutic process, for children affected by SC. The lack of a

common strategy shows how different are outcomes all around the countries, and the hospital centres.

Although SC is the most common cause of chorea in childhood, the number of cases is limited, so that the most part of the work can be done by retrospective studies. It becomes primary to outline a common line of gestion for these patients, so that the outcome can be the best, by reducing the time of hospitalization.

In conclusion, SC is still an important health problem. Although it is known as a benign, self-limiting condition, it has high morbidity especially in those patients with recurrent and persistent SC. SC can occasionally be misdiagnosed as a “fidgety” child or as a psychiatric manifestation, but it is important to diagnose, principally because a regular use of penicillin prophylaxis can reduce the risk of recurrence of SC and also prevent rheumatic heart disease and morbidity from neuropsychiatric effects.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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