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Original article

Management, treatment, and clinical approach of Sydenham's chorea in children: Italian survey on expert-based experience

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ABSTRACT

Sydenham's chorea (SC), an autoimmune disorder affecting the central nervous system, is a pivotal diagnostic criterion for acute rheumatic fever. Primarily prevalent in childhood, especially in developing countries, SC manifests with involuntary movements and neuropsychiatric symptoms. Predominantly occurring between ages 5 and 15, with a female bias, SC may recur, particularly during pregnancy or estrogen use. The autoimmune response affecting the basal ganglia, notably against dopamine, underlies the pathophysiology. Clinical management necessitates an integrated approach, potentially involving immunomodulatory therapies.

To address discrepancies in SC management, a survey was conducted across Italy, targeting specialists in neurology, pediatrics, child neuropsychiatry, and rheumatology. Of the 51 responding physicians, consensus favored hospitalization for suspected SC, with broad support for laboratory tests and brain MRI. Treatment preferences showed agreement on oral prednisone and IVIG, while opinions varied on duration and plasmapheresis. Haloperidol emerged as the preferred symptomatic therapy. Post-SC penicillin prophylaxis and steroid therapy gained strong support, although opinions differed on duration. Follow-up recommendations included neuropsychological and cardiological assessments.

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Despite offering valuable insights, broader and more studies are needed in order to guide treatment decisions in this well-known yet challenging complication of acute rheumatic fever, which continues to warrant scientific attention and concerted clinical efforts.

1. Introduction

Sydenham's chorea (SC), or rheumatic chorea, is a post-infectious autoimmune disease that affects the central nervous system and represents one of Jones' major criteria for the diagnosis of acute rheumatic fever (ARF). Such disease in turn results from a likely autoimmune response to a streptococcal β-hemolytic group A (SBEGA) pharyngeal infection.

SC is the most common acquired chorea in childhood globally, with a higher incidence in developing countries, and is characterized by involuntary movements, hypotonia, emotional lability, and other neuropsychiatric symptoms that require careful management and targeted treatment, even after the acute phase [1–3].

The disease commonly presents between the ages of 5 and 15, with an incidence peak at 8–9 years and a female predominance. Notably, SC can also recur, especially during pregnancy or estrogen use, indicating a connection with female sex hormones [3].

The pathophysiology involves an immune response affecting the basal ganglia. Anti-neuronal antibodies, particularly those targeting dopamine, seem to play a significant role. Interestingly, immunological and neuroimaging studies have supported the correlation between SC and the dopaminergic system [4].

The clinical management of SC requires an integrated approach, that can eventually include the use of immunomodulatory and immunosuppressive therapies. Despite its longevity and recurring challenges, the disease need global consensus among clinicians to improve treatment effectiveness.

In order to achieve a more profound understanding of the disease, along with the potential similarities and differences in the diagnostic and therapeutic processes of SC, we have enlisted a team of Italian specialists, encompassing neurologists, child neuropsychiatrists, pediatric neurologists and pediatricians, with the overarching aim of identifying a shared and cohesive management strategy.

2. Materials and methods

The study involved an online questionnaire hosted on a dedicated portal, consisting of 43 multiple-choice questions, which utilized a response scale that allowed participants to express their agreement with statements using options such as "strongly agree," "agree," "neutral," "disagree," or "do not know/do not respond". Additionally, each participant had the opportunity to provide a brief comment to elucidate their response. A consensus towards agreement or disagreement of a statement was assessed by reaching at least 75 % of responses.

The survey targeted clinicians with several years of experience in diagnosis and management of SC, affiliated with the Italian Societies of Pediatric Neurology (SINP), Pediatric Rheumatology (REUMAPED) and Child Neuropsichiatry (SINPIA).

The data collection period spanned from February to June 2023, during which recruitment efforts focused on ensuring a diverse participant pool, reaching out to professionals with varying clinical backgrounds. The online platform facilitated a seamless and efficient means of gathering responses, ensuring the study's comprehensive and timely data acquisition.

Moreover, to address potential bias, survey questions were neutrally designed, and data analysis employed a blinded review process for enhanced objectivity. Emphasizing honest reporting aimed to minimize bias, collectively enhancing the reliability and validity of our study findings on Sydenham's Chorea.

3. Results

A total of 51 physicians answered to our questionnaire, a summary of the results is presented in Fig. 1.

3.1. Diagnostic approach

In the first section, pertaining to the diagnostic process of SC, responses were largely concordant. In particular, most specialists support the hospitalization of patients with suspected SC for diagnostic purposes and initial therapeutic interventions, with over 82 % consensus. Additionally, the survey revealed a shared consensus towards the performance of laboratory tests such as pharyngeal swab for the detection of SBEGA (92.1 %), measurement of anti-streptolysin O titer (ASLO) (92.2 %), anti-DNase B (86.3 %), as well as the assessment of an autoimmune panel encompassing anti-nuclear antibodies (ANA), anti-extractable nuclear antigens (ENA), anti-thyroperoxidase (anti-TPO), and anti-thyroglobulin (anti-TG), in addition to screening for celiac disease (total serum IgA and anti-transglutaminase IgA levels), deemed necessary by 90.2 % of participants. Further laboratory investigations, such as screening for thrombophilia, serum copper and ceruloplasmin levels, and anti-phospholipid antibodies (anti-APL), were equally regarded as complementary in the diagnostic process. However, opinions differed on the measurement of serum and CSF levels of anti-DR2/DR3 antibodies and anti-neuronal antibodies (e.g., NMDAR, LGI1). Lastly, 43.1 % expressed neutrality regarding the execution of a genetic panel for movement disorders, with a significant number of participants remaining neutral.

Interestingly, the involved specialists exhibited less unanimity regarding the use of instrumental tests in the diagnostic process, such as cranial computed tomography (CT) (72.6 % disagreed) and electroencephalogram (EEG) (37.5 % disagreed, 29.4 % neutral), while cranial magnetic resonance imaging (MRI) emerged as the most recommended examination (86.3 %).

3.2. Therapeutic management

Concerning the therapeutic management section, participants exhibited a difference in opinions on several aspects, indicating a lack of consensus. Responses regarding the use of intravenous corticosteroids were notably heterogeneous, with no clear consensus. However, there was some agreement on the oral prednisone therapy at 1–2 mg/kg/day, endorsed by 60.8 % of participants. In contrast, oral betamethasone (0.1–0.2 mg/kg/day) received minimal support, with 39.22 % of responders disagreeing with its use. Opinions on treatment duration also varied, with a significant number of physicians opposing both excessively short (less than 2 weeks, 58,82 %) and prolonged (over 3 months, 62,75 %) durations. More than half of the participants (51.88 %) advocated for cessation timing based on clinical response, indicating a preference for personalized treatment plans Fig. 1B.

Intravenous immunoglobulin (IVIG) at a cumulative dosage of 2 g/kg administered over 2–5 days emerged as a recommended treatment for SC by 62,75 % of participants, either as an alternative or in addition to steroids. Conversely, there was widespread opposition to the use of plasmapheresis or other immunosuppressants as a first-line therapy, despite 56.3 % endorsing the latter in cases of first-line treatment failure.

Except for haloperidol, which was preferred by 64.7 % of participants, there was no distinct preference for any of the proposed drugs for symptomatic therapy for SC, including valproic acid (47.06 %),

carbamazepine (27.45 %), or pimozide (31.4 %).

Post-SC penicillin prophylaxis is deemed necessary by 78.1 % of involved physicians. Half of the respondents advocated for its continuation for 5 years, even in the absence of carditis, whereas 37.5 % recommended extending the treatment up to 18 years of age.

3.3. Follow-up

Finally, concerning the follow-up, the majority of participants find the utilization of neuropsychological tests beneficial (86.3 %), along with subsequent psychological (78.4 %) and cardiological (88.2 %) support. However, there is a consensus that additional laboratory tests (serial measurement of ASLO) or instrumental assessments (EEG or

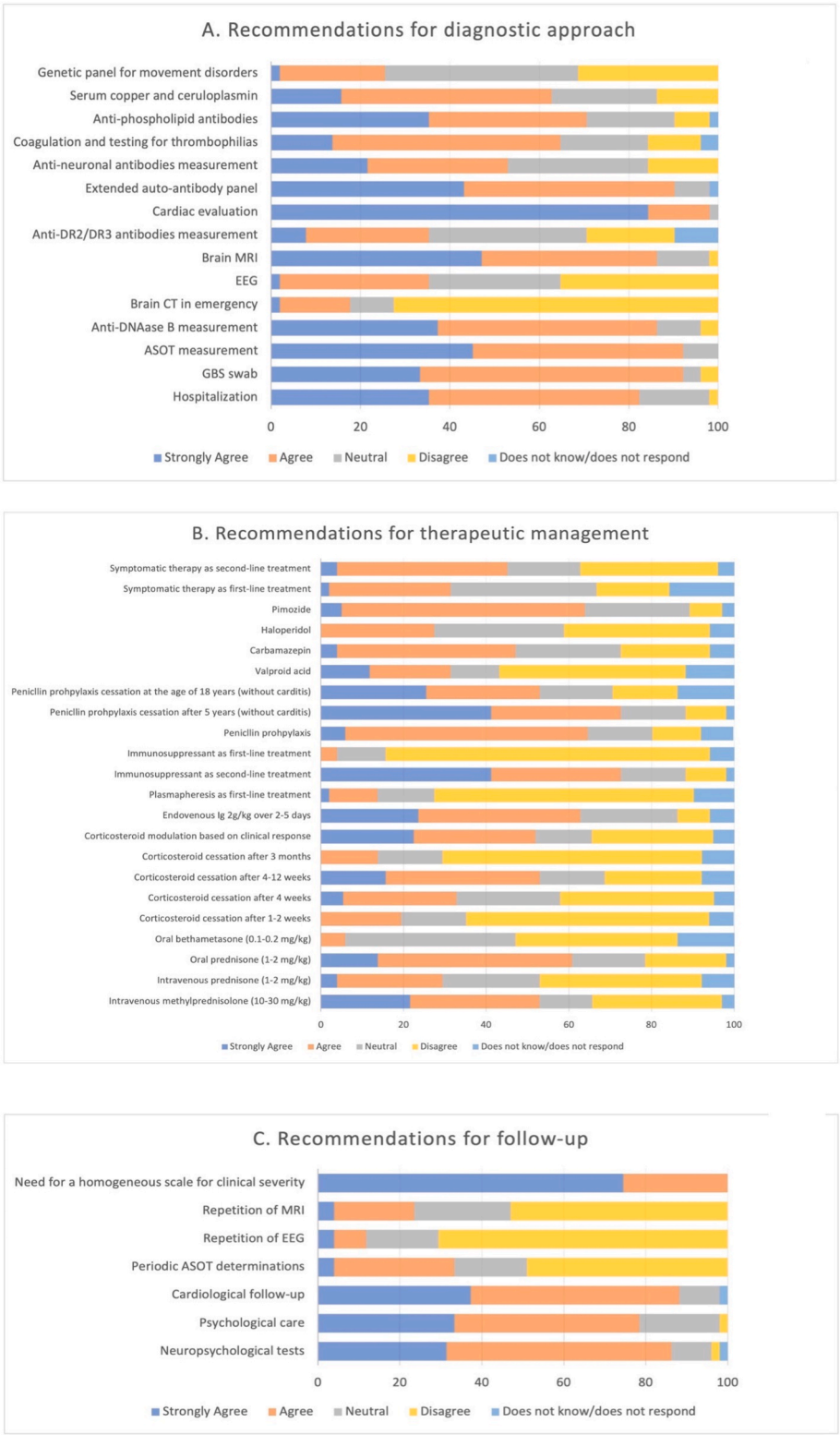

Fig. 1. Graph showing the level of agreement among medical professionals regarding diagnostic and therapeutic management of SC.

cerebral MRI) are not considered necessary. It is noteworthy that all participants consider the usefulness of a standardized and validated scale for assessing the severity of choreic symptoms to be useful.

4. Discussion

Sydenham's chorea represents a relatively common complication of acute rheumatic fever in the pediatric population, manifesting in 40 % of cases [5]. Consequently, it constitutes a major concern for child neuropsychiatrists and pediatric neurologists. However, its etiopathogenetic mechanism remains unclear, and its clinical management is still matter of debate, further complicated by the variable global prevalence of ARF globally. Our analysis provided an insightful perspective for identifying challenges in the management of this condition.

Participants generally concurred on the necessity of hospitalization, likely driven by the imperative need for differential diagnosis testing. We observed an almost unanimous agreement on the execution of tests for diagnosing SC and, if applicable, ARF. These tests include swabbing for streptococcal bacteria, assessing ASLO titer and anti-DNase B levels. Such markers, capable of persisting for months, may find diagnostic support in escalating titers indicative of recent streptococcal infection.

The survey respondents uniformly endorsed the use of other hematological tests, perhaps due to their cost-effectiveness and widespread availability for facilitating the process of differential diagnosis. Presumably motivated by similar considerations, invasive techniques for cerebrospinal fluid marker detection or the utilization of anti-DR2/DR3, owing to their limited prevalence and specificity, were less prevalent in their clinical practice [6–8].

In accordance with existing literature, MRI emerges as the most frequently employed neuroimaging modality, despite the absence of scientifically recognized pathogenetic signs definitively confirming the diagnosis [9].

Lastly, aligning with current guidelines, the overwhelming majority of participating physicians deem a cardiological evaluation indispensable for patients presenting with SC [10].

Regarding treatment, in line with current guidelines, the involved professionals expressed a moderate consensus for immunosuppressive therapy during the acute phase of the disease, specifically the administration of oral prednisone at a dosage of 1–2 mg/kg/day. It is interesting to note that the physicians were less unanimous in specifying a standard duration of therapy. A significant percentage (62.75 %) opposed cessation immediately following the acute phase, favoring extended treatment. Opinions diverged as well on ending treatment within the first four weeks, with 37.25 % against and 33.33 % in favor, reflecting differing clinical judgments and interpretations of the evidence. A modest majority (52.94 %) supported concluding therapy between 4 and 12 weeks, suggesting a perceived balance between therapeutic benefits and side effects. However, a considerable portion of participants (62.75 %) opposed cessation before three months, highlighting concerns over long-term outcomes and side effects of prolonged treatment. Indeed, current literature shows no major agreement on this matter as well. The lack of consensus on the duration of therapy may reflect the current lack of a robust evidence base for immunotherapy, aside from corticosteroid therapy, and symptomatic pharmacotherapy. This uncertainty highlights the need for more comprehensive clinical studies and trials to establish standardized treatment protocols. Despite this, corticosteroids have consistently demonstrated beneficial effects in reducing the duration of SC, suggesting they are currently the most reliable option available.

Concerning this aspect, a randomized double-blind parallel study conducted by Paz et al. investigated the utility of steroids in SC in a controlled setting. In this study, 37 pediatric and adolescent patients were randomly assigned to receive either a placebo or prednisone at a dosage of 2 mg/kg per day for four weeks, followed by a gradual tapering regimen. Both cohorts showed improvement over time; however, the prednisone-administered group demonstrated a swifter and earlier attainment of complete remission (54 days vs. 120 days). Comparable rates of relapses were documented across the two groups, with no instances of severe adverse events observed in the prednisone-treated cohort [11]. These observations underscore the importance of corticosteroids in the therapeutic regimen, even as the medical community continues to explore and refine additional treatment strategies to enhance patient outcomes.

Regarding additional therapeutic strategies, participants showed greater consensus on the administration of IVIG either as an alternative or in addition to corticosteroid therapy. The use of immunoglobulins in SC is still relatively unexplored in the literature, but some studies appear promising. In a randomized clinical trial by Walker et al., the effectiveness of standard SC management was compared with that of additional intravenous immunoglobulin (1 g/kg per day for 2 days) in two cohorts comprising 10 children. Evaluation of outcomes was conducted through a clinical rating scale, brain single-photon emission computed tomography, and the duration of symptomatic treatment. Interestingly, the IVIG cohort showed improved outcomes according to all three assessment tools [12]. Another study by Van Immerzeel et al. reported the cases of two girls, aged 11 and 13, treated with a five-day regimen of IVIG at a dosage of 400 mg/kg/day. The treatment was well-tolerated and exhibited a marked positive impact. In fact, shortly after administration, all signs and symptoms disappeared in both patients [13].

The use of plasmapheresis in SC patients in the literature is anecdotal [14,15], which likely justifies the limited inclination among the surveyed physicians to its administration. As for immunosuppressants, there is a stark contrast in their acceptance as a first-line option versus a second-line therapy. While a surprising 78 % are against it as an initial choice, 65 % support its use as a second-line medication, illustrating a pragmatic approach to escalating care in refractory cases.

However, it must be specified that despite the likely autoimmune pathogenesis, some Authors have questioned the resort to certain immunomodulatory therapeutic regimens, primarily due to their side effects and the potential predisposition to infections.

Interestingly, post-SC penicillin prophylaxis was considered necessary by 78.1 % of involved physicians However, the duration of such prophylaxis is subject to debate, with only 50 % advocating for its continuation for 5 years, even in the absence of carditis, whereas 37.5 % wish to prosecute the treatment up to 18 years of age. Regarding this aspect, it should be highlighted that according to guidelines, a longer prophylaxis is required for patients diagnosed with acute rheumatic fever and carditis, and those with acute rheumatic fever in the absence of carditis undergo a secondary prophylaxis of lower duration. The present survey was not directed to the analysis of acute rheumatic fever but has a specific focus on SC; therefore, as there is no uniform indication for the duration of secondary prophylaxis in this category of patients, it is not surprising that our survey did not evidence a complete agreement. Additionally, this question was designed to investigate the attitude of clinicians beyond guidelines, aiming to explore the depth of divergence between clinical practice and established guidelines. The responses indicate significant variability in clinical approaches, highlighting a slight gap between standardized recommendations and individual clinical judgments.

In examining support therapies, valproic acid received more approval compared to carbamazepine, yet neither reached a major consensus; it is important to note that a good portion remained neutral on this topic. On the other hand, haloperidol, a more traditional choice for chorea, is supported by nearly 65 % of respondents, resonating with its established place in clinical practice. Interestingly, findings from a retrospective 2020 study by Direk et al., involving 140 patients diagnosed with SC, revealed that 40 individuals initially selected haloperidol as their primary medication, and remarkably, they continued its usage despite experiencing side effects. However, it is noteworthy that, within this study, haloperidol exhibited the highest frequency of side effects compared to other assessed medications. On the other hand, valproate emerged with superior outcomes, proving effective as both a first and

second choice in the same study [16].

Pimozide, though considered by some, did not achieve clear consensus, with a significant proportion of respondents remaining neutral or undecided, perhaps reflecting its generally prevalent administration in more severe presentations of Sydenham's Chorea, as documented in the literature [17,18], and the heightened likelihood of severe side effects, which becomes particularly pronounced with prolonged treatment duration [16]. Of note, current literature reports levetiracetam, phenobarbitone, or diazepam as reasonable alternatives in cases of SC, perhaps for their anti-inflammatory and neuroprotective effects as well [16,19,20].

While there could be still an intriguing debate on therapeutic strategies, the opinion seems to be more unanimous regarding the clinical monitoring, management, and follow-up of patients.

The administration of neuropsychological tests in patients with SC received overwhelming support, with 86.27 % of specialists advocating for it, reflecting a common belief in their critical role in patient management. Psychological care also garnered substantial endorsement, with 78.43 % of participants acknowledging its appropriateness, underscoring the recognition of mental health in the holistic treatment of the disease. Cardiological follow-up was advised regardless of carditis at clinical onset, with 88.23 % agreement among the experts, indicating a strong inclination towards vigilant cardiovascular monitoring in these patients. Conversely, our survey revealed a division regarding the utility of periodic determinations of the anti-streptolysin O titer during follow-up, with a majority of 49.02 % opposing the practice, suggesting a lack of consensus on its effectiveness. Additionally, the appropriateness of repeating EEGs during follow-up was met with substantial opposition.

As with any study, limitations should be considered. The self-report format of the questionnaire introduced the potential for bias, as the results are subject to the individual preferences and experiences of the participating physicians. Furthermore, the relatively small sample size may contribute to an overestimation or underestimation of specific practices. However, the diverse backgrounds and specialties of the participating physicians add breadth to the study, offering insights from various perspectives within the medical field. While the sample size is relatively modest, it is reflective of the challenges inherent in gathering responses from specialized professionals. Despite these limitations, the study provides a valuable snapshot of current practices and opinions among physicians regarding the diagnosis and management of Sydenham's Chorea.

5. Conclusions

Our analysis emphasized consensus on hospitalization and key diagnostic tests performed in pediatric patients with SC, with MRI emerging as the preferred neuroimaging modality, as well as the general consensus on their follow-up. On the other hand, treatment preferences exhibited variability among physicians, since it could be influenced by factors such as side effects, cost considerations, and disease severity. We believe that the subjective nature of these regimens warrants a comprehensive review. Higher-level studies are needed to guide physicians in making informed and objective treatment decisions in the future. Particularly notable is the imperative, given Italy's intermediate-risk status for ARF, to formulate a precise clinical strategy for effectively managing Sydenham's Chorea.

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Conflict of interest

The authors declare no conflict of interest.

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