Rheumatic Chorea: Relationship to Systemic Manifestations and Response to Corticosteroids

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Objective To describe Sydenham chorea among children in a cohort of patients with rheumatic fever (RF).

Study design An existing database was used to identify demographic characteristics, clinical manifestations, and therapy in persons with RF identified in Salt Lake City, Utah, from 1985 through January 2002.

Results Of 584 cases in the database, 537 (91%) were new-onset RF (median age of 10 years) and 177 (33%) had chorea. Patients with chorea were more often female (OR = 0.37, 95% CI = 0.25-0.55, $P < .0001$) and were less likely to have carditis or arthritis. Prednisone treatment may lead to a shortened course of chorea (4.0 weeks in prednisone-treated [n = 32] vs 9.0 weeks in untreated [n = 14]; $P < .0001$). Among 33 patients seen at a median of 10.3 years (range 6.3-14.9 years) after their initial bout of chorea, 20% reported residual tremor or mood swings. Ten of the 33 (30%) had one or more recurrences of chorea.

Conclusions Chorea affected one-third of the children with RF. Patients with chorea were less likely to have severe cardiac or rheumatologic complications of RF. Therapy with prednisone shortened the duration of rheumatic chorea; some reported recurrences of chorea and had minor neurologic sequelae. *(J Pediatr 2007;151:679-83)*

Though the clinical features of rheumatic chorea have been recognized since the 17th century, when Thomas Sydenham first described chorea, current knowledge of the pathogenesis and outcome of the disorder is a product of 20th-century medical science.[1,2] Clinical and laboratory observations indicate that rheumatic chorea is the result of an immunopathologic response to an antecedent infection with the group A β-hemolytic streptococcus (GAS).[1] The neurologic complications of RF, of which chorea is the predominant feature, have been proposed to result from circulating antibodies that perturb the basal ganglia effects on motor control, especially in the caudate and subthalamic nuclei.[2,3]

Beginning in the early to mid-1980s, the Intermountain region of the United States has experienced the resurgence and persistence of RF.[4,5] During this time, cases have been entered into a registry maintained by the Division of Pediatric Cardiology, University of Utah; this registry currently represents one of the largest cohorts of RF cases in the United States in the last four decades, since the report of Jones and Bland in 1952.[6] The purpose of this report is to describe the clinical features of patients with chorea and to summarize the effects of treatment in a subset of this cohort.

METHODS

Study Population

The database of the Division of Pediatric Cardiology of the University of Utah and Primary Children's Medical Center (PCMC) contains nearly all cases of RF evaluated at PCMC since the early 1980s.[4,5] PCMC, the principal site for the clinical activities of the University of Utah Department of Pediatrics faculty, serves the Intermountain region, a referral base consisting currently of >1.5 million persons 21 years of age or under in Utah and portions of Idaho, Wyoming, Nevada, Colorado, and Montana. This study was approved by the Institutional Review Board of the University of Utah.

Identification of Cases

Cases of RF were diagnosed using the revised Jones and/or updated Jones criteria.[7,8] Subjects with suspected RF underwent a standard evaluation that consisted of echocardiography and direct examination by pediatric neurologists and/or experienced pediatric cardiologists to establish the diagnosis. The majority of subjects also had streptococcal

GAS	Group A β-hemolytic streptococcus	RF	Rheumatic fever
PCMC	Primary Children's Medical Center		

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Table I. RF cases with or without chorea and relationships to sex, age, and presence of carditis or arthritis

	Chorea (%)	No chorea (%)	OR	95% CI	*P* value
N	177	360			
Female	115 (65)	147 (40)	0.37	0.25-0.55	<.0001
Carditis (Total)	71 (40)	237 (66)	0.35	0.24-0.51	<.0001
Mild	62 (35)	134 (37)	0.54	0.36-0.80	.002
Moderate	7 (4)	55 (15)	0.15	0.06-0.34	<.0001
Severe	2 (1)	48 (13)	0.05	0.01-0.20	<.0001
Arthritis	18 (10)	232 (64)	0.06	0.03-0.11	<.0001
Mean age (years)	10.3	9.9			.21

serologies (anti-streptolysin O, anti-DNAse B) and inflammatory markers (sedimentation rate, C-reactive protein). Information extracted from the database included: age, sex, other associated features (presence and severity of carditis, arthritis), and whether the episode was new or recurrent chorea. The severity of carditis was defined as mild (clinically evident without radiographic cardiomegaly or heart failure), moderate (clinically evident with cardiomegaly but no heart failure) or severe (cardiomegaly and clinical heart failure).[5,9]

The list of patients with RF and chorea was then matched against the medical records of the Division of Pediatric Neurology to obtain additional details regarding the form (hemichorea [unilateral] or generalized), treatment, and duration of chorea. Follow-up telephone contact was made by the pediatric neurologist or mid-level provider at approximately 2-week intervals until the patient or parent indicated complete resolution of chorea. Given the retrospective nature of this report, follow-up information was variable. After their initial evaluation, patients with RF were typically returned to the care of their pediatricians.

Statistical Analysis

Dichotomous categorical variables were compared using crude and adjusted ORs and their 95% CIs or Fisher's exact test. Interaction between age and sex was tested by the Breslow-Day Test for Homogeniety of ORs across strata. Crude relative risk ratios and their 95% CIs were calculated for polychotomous nominal variables using multinomial logistic regression. Depending on the normality of the distributions, continuous variables for different patient groups were compared using the Unpaired *t* test and the Mann-Whitney test. All statistical analyses were calculated using STATA SE version 8.2 (Stata Corp., College Station, TX).

RESULTS

Demographics

The database contained 584 cases of RF identified between January 1, 1985 and January 1, 2002. Of these, 537 were new-onset cases of RF and 47 (9%) were recurrent RF. Case patients ranged in age from 2 to 21 years (median age of 10 years) at the onset of the RF. Slightly more than one-half of the patients with new-onset RF were male (51.2%). The vast majority of patients resided in and around the State of Utah.

Clinical Features

Table I summarizes relationships between chorea, sex, and selected clinical features of RF. Of the 537 case patients of new-onset RF, 177 (32%) had chorea. There was a female predominance among patients with chorea; 65% were female. Overall, 115 of the 177 case patients with chorea were female versus 147 of 360 case patients without chorea (OR = 0.37, 95% CI = 0.25-0.55, $P < .0001$).

Of 177 cases of new-onset rheumatic chorea identified in the database, 102 (58%) were evaluated in the pediatric neurology clinic and had medical records available for review. Patients with mild chorea were generally not seen by the pediatric neurologists. Of the 102 patients, 58 (57%) had generalized chorea and 43 (42%) had hemichorea. In one patient the type of chorea was not recorded. Of patients with hemichorea, 32 (74%) had right-sided chorea.

Cases with chorea were less likely to have other systemic manifestations of RF; ORs and their significance are listed in Table I. Many cases with chorea did not have cardiac involvement or had a less severe cardiac phenotype. We observed statistical differences in the prevalence of mild carditis in cases with or without chorea (OR = 0.54, 95% CI = 0.36-0.80, $P < .002$.). Moderate carditis was observed in 7 of 177 cases with chorea versus 55 of 360 cases without chorea (OR = 0.15, 95% CI = 0.06-0.35, $P < .0001$), and severe carditis was observed in only 2 of 177 cases with chorea versus 48 of 360 cases without chorea (OR = 0.05, 95% CI = 0.01-0.22, $P < .0001$). Conversely, patients with carditis were less likely to have chorea, and the more severe the carditis, the stronger this negative association. Patients with arthritis were also much less likely to have chorea (OR = 0.06, 95% CI = 0.03-0.11, $P < .0001$; Table I). Only 13 case patients (2.4%) had chorea, carditis, and arthritis in combination. Case patients with chorea were slightly older than case patients without chorea, but this difference was not statistically significant. ($P = 0.21$; Table I and Figure).

Treatment and Outcome

There was no specific protocol for treating rheumatic chorea during the study interval. A subset of patients with

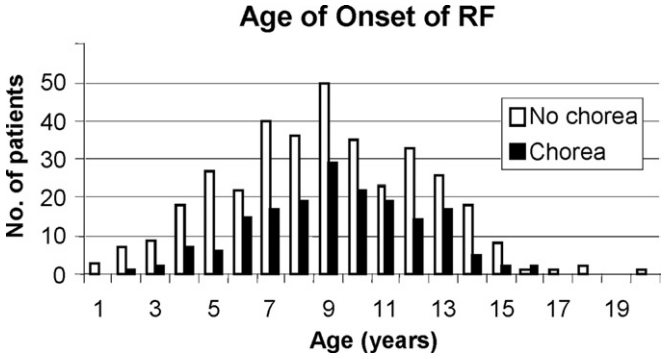

Figure. This bar graph shows the age distributions of children with and without chorea. No statistical differences were observed.

severe chorea (movement disorder that limited ambulation or self-feeding) was treated. Of the 102 chorea patients, 48 (47%) were treated with prednisone, 10 (10%) received haloperidol or sodium valproate, and 44 (43%) were not treated with medications. Fifty-two of the 102 (51%) had sufficient recorded follow-up information to determine the time to resolution of the chorea. These included 32 prednisone-treated and 14 non-pharmacologically treated patients. Six received other treatments, as above. Compared with patients who were not treated with medications, prednisone-treated patients had a shortened course of chorea (median of 4.0 weeks vs 9.0 weeks [Table II]). The small number of patients treated first with other medications precluded additional comparisons. The group with outcome data was 67% female and had a mean age 10.7 ± 3.1. The group without follow-up was 56% female with a mean age 9.9 ± 2.9. These groups were not statistically different from each other in both sex and age; $P = .72$ and $P = .21$, respectively.

Several additional associations were analyzed. These included associations between: sex and form of chorea (generalized vs unilateral); sex and treatment of chorea; treatment of chorea and form of chorea; treatment of chorea and presence of carditis; and presence of carditis and length of chorea. No additional statistically significant associations were identified.

Long-Term Outcome

Patients with a history of rheumatic chorea were invited to participate in a follow-up study to assess residual neurological abnormalities. Thirty-three were seen at a median of 10.3 years (range of 6.3 to 14.9 years) after their initial bout of rheumatic fever. Of these 33 case patients, 24 (73%) were female. Nine of 23 (40%) reported personality changes and 3 of 29 (10%) had obsessions or compulsions in association with their original episodes of chorea (not all items were recorded for all patients). Six of 32 (20%) noted neurological sequelae, consisting of mood swings or tremor, and 10 of 33 (30%) had minor neurological abnormalities, consisting of tremor, adventitious movements or hyperreflexia. Ten of the 33 subjects (30%) reported between one and six recurrences of chorea (5 of the 10 reported only one recurrence).

Table II. Prednisone therapy and duration of chorea

	Prednisone therapy	Untreated	*P* value
N	32	14	
Mean duration of chorea (wk)	4.8	11.7	
Median duration of chorea (wk)	4.0	9.0	<.001*
Range (wk)	1.0-16.0	4.0-24.0	
95% CI (wk)	3.5-6.1	7.9-15.5	

*Mann-Whitney U test.

DISCUSSION

This report confirms that chorea remains a common manifestation of RF, affecting approximately one-third of patients. The prevalence of chorea in children with RF varies, however, depending on the geographic location of the study cohort. In prior US reports the prevalence of chorea in RF has ranged from as low as 5% in New York City[10] and 7% in Hawaii[11] to as high as 30% in western Pennsylvania.[12,13] These data can be compared with low prevalence rates in Lebanon (2%),[14] moderate rates in New Zealand (11%),[15] Israel (13%),[16] Turkey (14%-19.7%),[17-19] and India (18.8%),[20] and high rates in Australia (28%)[21] and Brazil (30%).[22]

The reasons for regional variations in the prevalence of RF and chorea have not been determined. Differences in access to healthcare in general or to pediatric neurologists for consultation could lead to ascertainment bias in some regions. Other potential factors include differences in the strains of GAS or in the genetic predilections of human populations. Just as some strains, for example, the M3 and M18 serotypes, appear to be more rheumatogenic,[23] some strains may be more likely to cause chorea. Data from the Utah resurgence indicate that certain strains persist in environments for extended periods.[23,24] Familial clustering of RF occurs, but no consistent genetic polymorphisms that predispose persons to RF or chorea have been identified.

The diagnosis of rheumatic chorea is largely based on clinical criteria. In areas endemic for RF, such as the Intermountain West, rheumatic chorea is the most likely cause of chorea.[12] Our approach includes assessment of streptococcal serologies (anti-streptolysin O and anti-DNase B) and cardiology consultation for clinical evaluation and echocardiography. The majority of children with rheumatic fever have a specific echocardiographic pattern of mitral regurgitation, a feature providing strong support for rheumatic chorea. In rare instances, chorea associated with the anticardiolipin antibody syndrome or systemic lupus erythematosis can mimic rheumatic chorea.

RF and Sydenham chorea remain conditions of middle childhood; in virtually all reports, the median age of affected children has clustered around 10 years.[13,14,18,22,25] Young children (<5 years of age), as well as adults (>18 years of age), have low rates of RF, and in two studies, young

children with RF also had lower rates of chorea.[26,27] In the majority of studies, female patients compose approximately two-thirds of RF cases with chorea.

In the current study, there was an inverse relationship between the presence of chorea and the presence or severity of carditis or arthritis. Case patients with carditis and/or arthritis were less likely to have chorea than were case patients without carditis and/or arthritis (Table I). Similar observations have been made by Cardoso and colleagues in Brazil[28] and Carapetis and Currie in Australia.[21] It remains unknown whether such observations reflect ascertainment biases (eg, incomplete clinical assessments or not all symptoms being present concurrently because chorea occurs after a longer latency period following streptococcal infection than arthritis and acute carditis) or provide important clues regarding the molecular pathogenesis of RF and Sydenham chorea.

Because rheumatic chorea generally subsides spontaneously, pharmacologic therapy is reserved for patients with chorea that prevents independent ambulation, self-feeding, or causes high caloric expenditure and weight loss. Several different agents have been used, including carbamazepine, sodium valproate, haloperidol, and corticosteroids. Carbamazepine, haloperidol, and sodium valproate modify the dopaminergic or γ-aminobutryic acid (GABA) pathways,[29-33] whereas prednisone may directly affect the immunopathologic mechanism(s) that lead to neuronal dysfunction and chorea. Given a prior, adverse experience with haloperidol,[34] most child neurologists in Utah avoid this drug.

The case patients in this cohort who received prednisone were considered to have more severe symptoms than those who did not receive therapy. Despite this difference, retrospective analysis suggested that therapy with prednisone significantly shortened the duration of chorea by approximately 5.0 weeks. The use of prednisone in severe chorea is supported by a recent randomized, controlled trial[35] and several additional uncontrolled observations.[31-33] From a theoretical perspective, corticosteroid therapy can also be supported by the presumed immunopathologic pathogenesis of RF and chorea.[2,36] Studies have shown efficacy of high-dose corticosteroids in cases of refractory chorea and potential benefit from other immunomodulating therapies, such as plasmapheresis and intravenous immunoglobulin.[37] Although the initial bout of chorea remits with or without therapy, patients can have recurrences; 30% of a follow-up sample reported one or more recurrences.

The reasons for the persistence of RF in the Intermountain region of the United States are unknown. The major determinants of RF in developing countries cited by the World Health Organization, such as poverty, malnutrition, overcrowding, and a shortage of healthcare resources, do not apply to Utah and the surrounding states.[38] A unique interaction of GAS strains[23,24] and/or genetic predilections to RF may account for the ongoing RF resurgence in the Intermountain West.

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