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Pediatrics 2006;117;675-679; originally published online Mar 13, 2006;

DOI: 10.1542/peds.2005-1573

This information is current as of January 12, 2007

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Sydenham's Chorea in Western Pennsylvania

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. Chorea is characterized by involuntary, fleeting, irregular, nonrhythmic movements that flow from 1 body region to another. There are many causes of childhood chorea, including cerebrovascular accidents, collagen vascular diseases, drug intoxication, hyperthyroidism, Wilson's disease, Huntington's disease, and infectious agents. Although Sydenham's chorea (SC), a nonsuppurative sequela of group A streptococcal infection, is known to be a common cause of chorea, multiple laboratory and radiographic studies are often obtained to determine the cause of pediatric chorea. We conducted a retrospective chart review to determine the causes of childhood chorea seen in a large children's hospital in an area endemic for acute rheumatic fever (ARF). The utility of neuroimaging in establishing a final diagnosis of SC is discussed.

METHODS. Patients who received a diagnosis of chorea between 1980 and 2004 at the Children's Hospital of Pittsburgh were identified from databases that are maintained by the divisions of Infectious Diseases and Cardiology and from the hospital's medical records department. Charts were abstracted retrospectively. All patients who had new-onset chorea and did not have any underlying neurologic disorders were included in this study. Patient demographic, clinical, laboratory, and imaging information was analyzed. Follow-up information was not found consistently and therefore was not included. Charts of patients with questionable diagnoses were reviewed with a neurologist.

RESULTS. A total of 144 patients met the search criterion. Eleven patients had incomplete charts, and 6 charts could not be located. Thirty patients were excluded because they had preexisting neurologic diagnoses, eg, cerebral palsy. Fifteen patients were excluded because they were miscoded as having chorea. Eighty-two patients had new-onset chorea. The cause was SC ($n = 79$), postoperative cerebral ischemia ($n = 1$), and basal ganglion infarct ($n = 2$). Seventy-six (71%) children with SC were female. The mean age of presentation was 9.8 years (range: 5–14.5 years). Chorea was unilateral in 23 (30%) patients. Family history of ARF existed in 30% of patients. Neurologic symptoms of SC included behavior change (46%), dysarthria (67%), gait change (51%), deterioration of handwriting (29%), and headache (11%). Nonneurologic manifestations of ARF were carditis (44%), arthritis (11%), erythema marginatum (3%), and subcutaneous nodules (0%). Antecedent group A streptococcal infection was documented in 99% of patients

www.pediatrics.org/cgi/doi/10.1542/peds.2005-1573

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Key Words

streptococcal infection, Sydenham, Jones criteria, chorea, acute rheumatic fever

Abbreviations

SC—Sydenham's chorea
ARF—acute rheumatic fever
CHP—Children's Hospital of Pittsburgh
CT—computed tomography

Accepted for publication Oct 27, 2005

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who were tested by an elevated antistreptolysin O titer ($n = 53$), an elevated anti-deoxyribonuclease B titer ($n = 7$), a positive streptozyme ($n = 53$), or acute throat infection with *Streptococcus pyogenes* ($n = 19$). A total of 52 neuroimaging tests were obtained from 46 patients with SC. In patients with SC, brain MRI was abnormal in 8 of 32 patients, and brain computed tomography was abnormal in 1 of 20 patients. Abnormalities did not aid in diagnosis and included nonspecific increased signal ($n = 2$), nonspecific punctate lesions ($n = 2$), asymmetry of the hippocampal fissures, unrelated petrous bone anomaly, Arnold Chiari malformation, and medulloblastoma in a macrocephalic patient. Three patients with chorea that was not attributed to ARF had atypical presentations: 1 developed chorea after a perioperative hypoxic/ischemic central nervous system insult; 1 had an episode of disorientation, aphasia, and transient facial droop (angiography showed basal ganglia infarct); and 1 with hemichorea had basal ganglion infarct seen on MRI.

CONCLUSIONS. Ninety-six percent of children who had acute chorea and presented to a large children's hospital in an area that is endemic for ARF had SC. These patients had characteristic demographic and clinical features of SC. The most common concurrent major Jones criterion was carditis. Arthritis, erythema marginatum, and subcutaneous nodules were uncommon in this population. Neuroimaging was obtained in 58% of patients with SC and did not aid in any of their diagnoses. The 3 patients with chorea that was not caused by SC had histories that were atypical for SC and warranted neuroimaging. SC can be readily diagnosed on the basis of history, physical examination, and laboratory evaluation; neuroimaging is not necessary and should be reserved for patients who have an atypical presentation, including hemichorea.

CHOREA IS CHARACTERIZED by involuntary, fleeting, irregular, nonrhythmic movements that flow from 1 body region to another. There are many causes of childhood chorea, including cerebrovascular accidents, collagen vascular diseases, drug intoxication, hyperthyroidism, Wilson's disease, Huntington's disease, and infectious agents. One of the most common forms of childhood chorea is Sydenham's chorea (SC), a nonsuppurative sequela of group A streptococcal infection that typically presents as choreiform movements, muscular weakness, and behavioral changes.¹ It is a major manifestation of acute rheumatic fever (ARF) and, according to the 1992 modified Jones criteria, is sufficient evidence on which to base a diagnosis of ARF.²

The diagnosis of SC is challenging because onset of symptoms may occur 1 to 8 months after the predisposing streptococcal pharyngitis and, in some cases, long after laboratory evidence of group A streptococcal infection is present.³ The Jones criteria stipulate that other

causes of childhood chorea be excluded before SC can be diagnosed.² Although standard neurology and pediatric textbooks do not provide recommendations regarding the performance of neuroimaging in patients with chorea,^{4,5} Anouti et al⁶ recommended that most patients with chorea undergo imaging of the brain to disclose the underlying cause. We conducted a retrospective chart review to determine the causes of childhood chorea that were seen in a large children's hospital in an area that is endemic for ARF. The utility of neuroimaging in establishing a final diagnosis of SC is discussed.

METHODS

Patient records were obtained from 3 separate sources to capture all patients who presented with chorea: (1) medical records from Children's Hospital of Pittsburgh (CHP) were searched for a discharge diagnosis of "rheumatic chorea" with or without heart involvement and other "choreas" from 1991 through 2004 (searching of general medical records by diagnostic code was not available for 1980–1990), (2) the CHP Infectious Disease database was reviewed from 1980 to 2004 for patients with chorea, and (3) the computer database that is maintained by the Cardiology Division of CHP was searched for patients who had the diagnosis of chorea and presented between 1980 and 2004. Although the neurology division does not maintain a clinical database, they refer to the cardiology division all patients who present with chorea. Only patients with new-onset acute chorea were included. Patients were excluded when complete records were not available or when they had a previously recognized underlying neurologic disorder. Patients with learning disabilities were included in the study.

Patient demographic, clinical, laboratory, and imaging information was extrapolated from each medical record and entered into a standardized database. Follow-up information was not found consistently in the medical records and therefore was not analyzed. Medical records from patients with questionable diagnoses were reviewed and reevaluated with a neurologist.

The revised Jones criteria state that clinically silent cardiac abnormalities that are detected only by echocardiography should not be classified as carditis.² Recent studies have shown that pathologic and physiologic valvulitis can be distinguished by echocardiogram when strict guidelines are used.^{7,8} Because acceptance of clinically silent carditis is controversial, we adhered to the guidelines proposed by the Jones criteria.^{2,9} Carditis was defined by clinical evidence of mitral or aortic valvular disease.

RESULTS

Study Patients

A total of 144 patients met the search criterion. The charts of 6 patients could not be located, and 11 patients

had incomplete records. Thirty patients were excluded from the study because they had preexisting neurologic disorders, eg, cerebral palsy. Fifteen patients were miscoded as having chorea. Actual diagnoses for these patients included congenital cardiac defects without chorea in 3 patients; pneumonia in 2 patients; ARF without chorea in 2 patients; and asthma, cellulitis, nonspecific movement disorder, basal ganglion embolus without chorea, otitis media, systemic lupus erythematosus, truncal ataxia, and abdominal pain in 1 patient each. Eighty-two patients had chorea. The cause was SC associated with ARF in 79 patients, postoperative cerebral ischemia in 1 patient, and basal ganglion infarct in 2 patients.

Demographics and Other Features of Patients With Chorea

Fifty-six (71%) of 79 patients with chorea were female. The mean age was 9.8 years (range: 5–14.5 years). Fifty-five (70%) patients had generalized chorea, and 23 (30%) patients had hemichorea. Three patients incurred injuries before the onset of chorea. One patient had hit her head on a headboard 3 to 4 days before. Another patient fell off his bike onto his right arm and developed right-sided hemichorea shortly thereafter. The third patient developed hemichorea a few days after being kicked in the head.

Family history was available for 68 patients. Twenty-one (30%) patients had a family history of ARF. Twenty-three patients had a family history of neurologic disorders, including seizures (13), Parkinson's disease (3), Huntington's disease (2), neurofibromatosis (1), Bell's palsy (1), cerebral hemorrhage (1), tardive dyskinesia (1), and mental retardation (1).

Clinical and Laboratory Manifestations

Most patients with ARF had typical neurologic manifestations of SC, including changes in behavior, dysarthria, gait impairment, handwriting changes, headaches, and muscular weakness (Table 1). A few patients with ARF had less common symptoms, including 2 with facial

TABLE 1 Clinical Features of 79 Patients With SC Secondary to ARF Who Were Evaluated at CHP 1980–2004

Clinical Feature	No. of Patients (%)
Female	56 (71)
Hemichorea	23 (29)
Behavior changes	36 (46)
Speech changes	53 (67)
Handwriting changes	23 (29)
Gait changes	40 (51)
Headache	9 (11)
Muscle weakness	12 (15)
Carditis	35 (44)
Arthritis	9 (11)
Erythema marginatum	2 (3)
Subcutaneous nodules	0 (0)

droop, 3 with visual changes, 1 with emesis, and 1 with inward deviation of the right foot. One patient with ARF developed new-onset chorea 2 months after initially presenting with carditis and arthritis. Another patient presented with left-sided hemichorea, arthralgias, and gait changes. Laboratory evaluation was significant for positive throat culture and elevated erythrocyte sedimentation rate, streptozyme, and antistreptolysin O titer. Although there was no murmur on examination to diagnose carditis, echocardiography revealed mild mitral regurgitation from a thickened mitral valve, which further raised the suspicion for ARF. This patient also had increased head circumference, and MRI revealed a medulloblastoma. This patient therefore received a diagnosis of both medulloblastoma and SC.

Carditis was the most common major criterion that was concurrent with chorea in patients with ARF. Thirty-five (44%) patients had murmurs consistent with carditis. Nine (11%) had either a history of arthritis (7) or active arthritis (2) at the time of presentation, 2 patients (3%) had erythema marginatum, and none of the patients had subcutaneous nodules.

Laboratory evaluation for streptococcal infection was available for 71 patients with ARF. Streptococcal infection was documented in 70 (99%) patients who were tested by an elevated antistreptolysin O titer (53), an elevated anti-deoxyribonuclease B titer (7), a positive streptozyme (53), or acute throat infection with *Streptococcus pyogenes* (19). Twenty-four (36%) of the 66 patients tested had an elevated erythrocyte sedimentation rate or C-reactive protein. Acute-phase reactants are frequently normal in patients who present with chorea.

Imaging

Thirty-two patients with ARF had MRI of the brain performed. None of the 8 abnormalities (Table 2) that were seen on MRI revealed the cause of the chorea.

Twenty patients with ARF had a computed tomography (CT) of the head performed. Six of these patients also had MRIs. The only abnormal finding on CT was opacification of the mastoid air cells. This CT was obtained to delineate further the abnormal petrous bone found on MRI. One patient who had both a CT and an

TABLE 2 Abnormalities Found on MRI of the Brain in Patients With SC (N = 32)

Anomalies of the petrous bone
Medulloblastoma incidentally found in patient with increased head circumference
Asymmetry of the hippocampal fissures
Increased signal in the subcortical white matter of bilateral parietal areas
Punctate lesions in parietal lobe
Punctate lesions in frontal lobe
Increased signal in right globus pallidum and venous angioma in right cerebellum
Type I Arnold Chiari malformation

MRI performed had a history of head trauma before the development of chorea. Another patient had new-onset headaches and emesis. The final 3 patients had histories and physical examinations consistent with SC. In 1, the MRI showed an insignificant punctate lesion in the right parietal white matter.

Chorea That Was Not ARF

Three patients with chorea did not have ARF. One patient developed generalized chorea 4 days after cardiac surgery and was thought to have suffered a perioperative hypoxic/ischemic central nervous system insult. The second patient developed bilateral chorea after experiencing headaches for 10 months. Five days after the onset of chorea, the patient became disoriented and unable to speak for 5 minutes. Throat culture was positive for group A streptococcus, there were no other major Jones criteria, and MRI showed increased signal uptake in the left caudate and putamen. The constellation of clinical findings was thought to be consistent with SC. During the next 2 weeks, the patient developed neurologic symptoms, including transient facial droop, facial tingling, and inability to speak. An angiogram showed narrowing of the proximal left middle and anterior cerebral arteries, causing decreased blood flow to the left basal ganglion, thereby confirming a diagnosis of left basal ganglia infarct. The third patient had 6 days of left-sided hemichorea associated with emotional lability and gait disturbance. There was no laboratory evidence of streptococcal infection or elevated acute-phase reactants. The patient was found to have a basal ganglion infarct by MRI.

DISCUSSION

Seventy-nine patients with SC were identified. These patients had characteristic demographic and clinical features of the disease. As in all large series, there was a female predominance. A high familial incidence of ARF (32%) has been described and was observed in our study population.¹⁰ The predisposition to develop SC is not yet understood but does not seem to be associated with HLA class I or class II antigens.¹¹ Hemichorea was observed in 30% of patients, similar to the proportion documented in other populations.^{12,13} Other typical neurologic symptoms that are associated with SC were also apparent in our study population, including changes in speech, handwriting, gait, behavior, and muscular strength. Carditis was the most common major criterion that was concurrent in 44% of our patients. Because a large number of our patients were identified from the cardiology division's database, there may have been accrual bias that increased the apparent proportion of patients with cardiac involvement. Arthritis, erythema marginatum, and subcutaneous nodules were rare in our population, as in other reports.^{14,15}

SC follows infection with certain strains of group A

Streptococcus.³ Studies that layered sera that were obtained from patients with chorea over human brain have shown a striking pattern of immunofluorescence within cytoplasm of central nervous system tissue. Most of the reactivity occurs within the corpus striatum and is thought to be responsible for development of adventitious movements. However, there is also some degree of reactivity in the cerebral cortex that could be responsible for the associated emotional changes.¹⁶ Kirvan et al¹⁷ showed that chorea monoclonal antibodies have specificity for mammalian lysoganglioside and N-acetyl- β -D-glucosamine, the dominant epitope of group A streptococcal carbohydrate. These antibodies target the surface of neuronal cells and induce calcium/calmodulin-dependent protein kinase II activity. Neuropathologic studies in severely ill patients have shown changes such as inflammatory vasculitis, neuronal swelling, and petechiae most prominent in the basal ganglia but also involving the cerebral cortex and cerebellum.^{18,19}

MRIs, although often normal, have been reported to exhibit findings that support the metabolic and histologic changes that have been described in SC.²⁰ Findings reported on MRI include multiple foci of increased signal in the cerebral white matter, increased signal intensity in the caudate nucleus and putamen with mass effect on the adjacent right lateral ventricle, and enlargement of the right caudate and putamen.²⁰⁻²⁴ CT abnormalities, including low attenuation in the corpus striatum without mass effect and hypodensity of the right caudate, have been reported less frequently.^{21,23} Abnormalities that are seen on imaging of the central nervous system usually improve when chorea resolves; however, sometimes the injury is permanent. Because of the great variability of MRI and CT findings in SC, neuroimaging cannot be used to diagnose SC; they can be used only to exclude other causes of chorea. Three of our patients had subtle white matter changes, and 1 patient had increased signal in the right globus pallidum. These changes could have been a consequence of ARF, or they could have been incidental findings.

The data presented in this report indicate that SC is by far the most common cause of childhood chorea referral to a large children's hospital in an area that is endemic for ARF. In our study, 82 patients without previous neurologic diagnoses presented with choreiform movements over 25 years. Three of these patients did not have ARF. Their histories were atypical for what is commonly seen in SC; 1 of the patients had recently undergone cardiac surgery, 1 patient had intermittent episodes of facial droop coupled with inability to speak, and 1 patient had hemichorea associated with a basal ganglia infarct. Most of the patients with SC had classic symptoms of the movement disorder. Atypical histories included increased head circumference, emesis, hemifacial droop, visual changes, preceding head trauma, and inward deviation of the right foot. In these patients, ~13%

of the population, it was warranted to obtain images of the head to eliminate other causes of chorea. However, in all other patients, imaging of the brain did not yield information that contributed to diagnosis, management, or prognosis. SC can be diagnosed on the basis of history, physical examination, and laboratory evaluation. We therefore recommend that neuroimaging be obtained only in patients with unusual histories, including hemichorea (which, although not unusual, is less common), or inconsistent findings on physical examination.

ACKNOWLEDGMENTS

We thank D. Kathleen Colborn for technical help with data entry and Dr Ira Bergman for assistance with reviewing charts of patients with questionable diagnoses.

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This information is current as of January 12, 2007

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