A hundred years ago in the United States, rheumatic heart disease was the leading cause of death among school-aged and older children. In the 1930s, epidemiologic evidence established a link to hemolytic streptococcal pharyngitis. One of the most remarkable accomplishments of modern medicine has been the virtual eradication of acute rheumatic fever in high-income countries, attributed to a combination of public health measures and the discovery of penicillin.

Although chorea is 1 of the 5 long-accepted major Jones criteria for rheumatic fever, it is not widely appreciated that emotional or psychiatric features frequently went along with the abnormal movements. Or, as Sir Douglas Hubble wrote in 1943, “The personality of the rheumatic child shows a quantitative increase in emotion and kinesis—which has long been recognized by many clinical observers—and it is suggested that this nervous instability is an important factor in the development of the rheumatic state.”

In 1998, Swedo et al at the National Institute of Mental Health described a series of 50 children with evidence of group A streptococcal (GAS) exposure or frank pharyngitis who subsequently experienced the abrupt onset of obsessive-compulsive disorder (OCD) features and/or tics, and they coined the term PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections). None of these children went on to develop rheumatic heart disease or the other systemic features of acute rheumatic fever. However, after more than 25 years, a network of pediatric specialists is growing across the country in response to a tidal wave of children whose OCD, movement, and oppositional symptoms in previous decades would have landed them in the offices of child neurologists and psychiatrists.

In this issue, Ma et al share a longitudinal analysis of 193 children with PANS (pediatric acute-onset neuropsychiatric syndrome), a more broadly defined condition related to PANDAS. Retrospectively reviewing data on these young children with behavioral symptoms, they found a surprisingly high incidence of patients who developed arthritis over the average 4-year period of observation: 55 of the 193 children (28%) ultimately demonstrated features of arthritis, but not just any arthritis. They had an unusual rheumatic disease profile, with 31 of 55 children (56%) showing Achilles enthesitis, 35 (64%) with inflammatory back pain, and 38 (69%) with sacroiliac joint tenderness. Only 4 patients (2% of the entire cohort) developed the more typical childhood forms of arthritis, namely systemic lupus or juvenile idiopathic arthritis.

In my own patient population of almost 600 families, back pain is a very common concern—and it can be difficult to discern true spondyloarthropathy from the very common pain amplification findings associated with poor sleep (virtually universal among patients with PANS). Nevertheless, Ma et al performed musculoskeletal ultrasonography on 40 children with arthritis and found either effusions or synovitis in the vast majority. They did not specify which joints were examined, but the possibility of real back arthritis in so many of these children with behavioral problems is intriguing.

The authors did not discuss the impact that their treatments may have had on their findings. But patients with PANS are often prescribed multiple medications, and this may help explain the frequent elevation in antihistone antibodies (a marker commonly associated with drug-induced lupus and present in 16 of 82 children tested in this study [almost 20%]). The high prevalence of children with PANS symptoms and a coincident eating disorder (107 of 193 [55%]) remains unexplained. In my experience, two-thirds of these children have a history of abundant infections, which may help explain the frequent observation of elevated inflammatory markers (c-dimer, von Willibrand factor, platelet count, and erythrocyte sedimentation rate).
However, their provocative conclusion is that more than 30 years after most of the rheumatogenic strains of GAS appear to have been eliminated in high-income countries, certain children (and perhaps particularly those with a predisposition to spondyloarthropathy) may react to many kinds of community-acquired infections with the abrupt onset of tics, OCD, and other behavioral abnormalities that are classically associated with GAS pharyngitis. The spondyloarthropathies, probably more than all the other rheumatic diseases, are associated with infectious triggers, such as urinary pathogens in reactive arthritis, skin and gut dysbiosis in psoriatic arthritis, or the colonic flora in Crohn disease–related arthritis. So one may speculate that there could exist PANDA-genic strains of bacteria that may elicit these extreme behavioral and tic reactions in certain genetically susceptible hosts.

Certainly these and other researchers will continue to trace the link between infection and neurobehavioral symptoms back to the postulated misfiring of the basal ganglia area of the brain, which is clearly affected in rheumatic fever. About the mind-body connection in rheumatic fever, Sir Hubble wrote the following more than 80 years ago: “There is no disorder in which the emotional and the physical components seem more inextricably mingled. There is no disorder in which the attempt to separate the psyche from the soma, the functional from the organic, is more baffling. It is a long step from the undischarged emotion of the choreic child to the adult dying from congestive heart failure, and of many of the steps in this unhappy pilgrimage we are ignorant.”

ARTICLE INFORMATION
Published: July 30, 2024. doi:10.1001/jamanetworkopen.2024.21636
Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2024 Whelan JP. JAMA Network Open.
Corresponding Author: J. Patrick Whelan, MD, PhD, Department of Pediatrics, Division of Allergy, Immunology, and Rheumatology, University of California, Los Angeles, 200 Medical Plaza, Ste 265, Los Angeles, CA 90095 (pwhelan@mednet.ucla.edu).
Author Affiliation: Department of Pediatrics, Division of Allergy, Immunology, and Rheumatology, University of California, Los Angeles.
Conflict of Interest Disclosures: None reported.

REFERENCES