Epileptic Seizures As A Neurological Complication Of Reiter Disease

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Reiter syndrome is classically characterized as the clinical triad of arthritis, urethritis, and conjunctivitis. Similar disease entities have been previously described by Stoll in 1776 as of postenteric origin and by Brodie in 1818 as a postvenereal syndrome. The German hygienist Hans Reiter reported in 1916 a case in which a young lieutenant developed purulent urethritis, conjunctivitis, arthritis, and iritis after an episode of bloody diarrhea, and he named the condition "spirochaetosis arthritica." The term Reiter syndrome was formally described by Bauer and Engelman in 1942, and the reports of Paronen and Noer conclusively associated epidemic dysentery with the onset of Reiter syndrome.

Young adults are most commonly affected at a suggested male-female ratio of 5:1 or 6:1, and the disease onset peaks during the third decade of life. The increased occurrence of the histocompatibility antigen HLA-B27 in patients with Reiter syndrome has been known since 1973 and is found in 75 to 80 percent of all patients. Reiter syndrome is preceded by specific gastrointestinal or genitourinary infections, and there is a distinct geographic variation of the triggering infectious organism. In the United States and United Kingdom the posturethritic-venereal origin is the more common form, with Chlamydia trachomatis or Mycoplasma species as the precipitators of arthritis. In other parts of the world Shigella, Salmonella, and Yersinia species have been implicated in the postdysenteric form of the disease. The acute or subacute articular manifestations follow the triggering infectious episode with a latency period ranging from a few days to 3 weeks. The arthropathy is typically a rheumatoid factor-negative asymmetric oligoarthritis involving knees, ankles, and feet, and during the acute phase low back pain is an expression of acute sacroiliitis. The arthritis can progress in an additive fashion to involve the joints of the upper extremities. Inflammation of the bony attachments of tendons or fasciae (enthesopathy) is a further characteristic of Reiter syndrome. Involvement of the digits is occasionally accompanied by dactylitis (sausage digits). The typical extra-articular features of Reiter syndrome include mucocutaneous (oral ulcerations, keratoderma blennorrhagicum), urogenital (circinate balanitis, cervicitis, vaginitis), and ocular manifestations (conjunctivitis, uveitis, and keratitis).

Rare complications of Reiter syndrome include cardiac conduction abnormalities and aortic regurgitation in up to 10 percent of all patients, glomerulonephritis and renal amyloidosis, serositis, and pulmonary infiltrate. In addition, unusual neurologic and psychiatric conditions have been described in individual cases. The case presented here suggests the association of acute postdysenteric Reiter syndrome and transitory epileptic seizures with electroencephalographic changes.

Case Report

A 19-year-old male soldier was referred to an army outpatient clinic for evaluation of a 1-week history of bloody diarrhea. He had no history of gastrointestinal disorder or rheumatologic or neurologic disease. There was no known family history of mental or neurologic illness or arthritis. The patient denied any sexual activity or any history of sexually transmitted diseases. For the last 4 months he had been undergoing mandatory basic training in the army and living with other recruits in army tents.

One week after the onset of diarrhea he developed conjunctivitis and oral lesions, and a few days later painful swelling of the right knee and ankle occurred. There was no urethral discharge, but penile lesions appeared. The dysentery gradually subsided during the course of 10 days without any antibiotic treatment.

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The symptoms of peripheral arthropathy persisted for 6 weeks and were accompanied by tenderness of the right achilles tendon.

Two weeks after the onset of diarrhea he complained of drowsiness and headache that were followed by two witnessed episodes of generalized seizures. He was subsequently admitted to an army inpatient facility for further work-up and treatment.

On admission a mild bilateral conjunctivitis and erythematous oral mucosal lesions were noted. The right knee was swollen, tender, and warm, and the achilles tendon was painful on palpation. Findings of his cardiovascular examination were normal, and no heart murmurs were noted. On the shaft of the penis, distinct large, shallow, painless ulcerations were found. No further cutaneous lesions on the trunk or extremities were detected. The neurological and mental status examinations were unremarkable, and no deficits were found.

Laboratory data showed a white cell count of 12,000/mm³ with 64 percent segmented neutrophils, 25 percent band cells, 8 percent lymphocytes, and 3 percent monocytes. Hemoglobin was 12.4 g/dL and platelets were 216,000/mm³. The screening tests for sexually transmitted diseases, including human immunodeficiency virus, syphilis, chlamydia, and gonorrhea, were negative. Rheumatoid factor, serum antinuclear antibody titer, and anti streptococcal antibody titer were negative. Serum C3 and C4 concentrations were normal, and human leukocyte antigen (HLA)-B27 was found. A stool culture taken during the dysenteric episode of the disease was reported to disclose *Shigella flexneri*. Findings from the urinalysis were normal. An arthrocentesis of the right knee was performed on admission, and 20 mL of turbid fluid was aspirated. The liquid was Gram stain negative, and no microorganisms were cultured. The white cell count was 3500/mm³, consisting predominantly of polymorphonuclear cells.

The results of radiographic studies of the knees and ankles were reported as normal. A computed tomographic brain scan with and without contrast showed no pathomorphological changes, and the cerebrospinal fluid analysis was unremarkable. The electroencephalogram (EEG) showed two bifrontal epileptogenic foci, and the convulsions were diagnosed as secondary, tonic-clonic seizures. Carbamazepine was prescribed, and no seizures occurred during the 1-week hospitalization or the next 16 months of monthly outpatient follow-up, even after the discontinuance of the anticonvulsive treatment. His peripheral arthropathy was initially treated with ibuprofen, which was subsequently replaced with naproxen for marked clinical improvement.

A complete remission of Reiter syndrome was recorded within 4 months. An EEG was performed at 10 and 16 months after the first seizure episode and showed no paroxysmal activity or abnormality.

**Discussion**

The clinical diagnosis of Reiter syndrome is often difficult because its clinical features are shared by arthritides associated with enteric infections, inflammatory bowel disease, psoriasis, and ankylosing spondylitis and because the clinical triad of arthritis, nongonococcal urethritis, and conjunctivitis is observed in only about 30 percent of all patients with Reiter syndrome. The American College of Rheumatology (ACR) has therefore revised the requirements for the diagnosis of Reiter syndrome to peripheral arthritis of more than 1 month's duration, occurring in association with urethritis or cervicitis. These criteria have not been universally accepted, because of the substantial number of patients with postenteric or posturethritic arthritides without extra-articular manifestations, who are often HLA-B27 positive but failed to meet ACR criteria. In this context the broader concept of reactive arthritides has been introduced to define all clinical entities in which an inflammatory arthropathy arises at a site remote from the primary infection. This definition is restricted to conditions frequently associated with HLA-B27 and does not include arthritides associated with ulcerative colitis or regional enteritis, rheumatic fever, Lyme arthritis, Whipple disease, and postviral arthritides.

The arthritis of Reiter syndrome is considered as one clinical manifestation of reactive arthritis but is still distinguishable by its typical extra-articular features.

The postinfectious onset of acute arthritis in individuals with the same genetic predisposition implicated a specific bacteria-host interaction in susceptible hosts. Four possible arthritogenic mechanisms have been suggested: (1) altered...
bowel anatomy, (2) altered bowel permeability, (3) toxin-mediated synovitis, and (4) autoimmunity caused by molecular mimicry between HLA-B27 and various enterobacterial cell wall fragments.

According to this arthritogenic model the local inflammation of the bowel wall results in increased permeability of specific microbial and dietary antigens, which results in either an in situ antigen deposition, the induction of cellular and humoral immune response to the bacteria that crossreacts with cartilage, or perhaps an induced autoreactivity to HLA-B27 by which reactive arthritis might be triggered. The described mechanism of induced autoreactivity could explain the increased disease susceptibility, severity, and chronicity of arthropathy, as well as the extra-articular features in HLA-B27-positive patients. For the practicing physician the knowledge of the above-mentioned pathophysiologic mechanism forms the basis for the differential diagnosis of Reiter syndrome.

Acute diarrhea in the setting of arthritis can be differentiated by a triggering enteropathogenic bacteria, which is sometimes limited to certain species and serotypes. It is known, for example, that arthritic manifestations are associated with *Shigella flexneri* (serotype 2 or 2a) and with *Shigella dysenteriae*, but not following epidemic infections with *Shigella sonnei*. Various species of *Salmonella* paratyphi groups B, C, and D, *Salmonella typhimurium* and *enteritidis* have been found to be potentially arthritogenic, and reactive arthritis after *Yersinia* infections has been primarily attributed to *Yersinia enterocolitica* (serotypes 3,6,8,9).

Postdysenteric joint complaints in the absence of extra-articular features in HLA-B27-positive patients suggests a reactive arthritis. It is important to mention that HLA-B27 is a genetic marker found in 60 to 80 percent of patients with reactive arthritis following *Shigella, Salmonella, Yersinia*, and *Campylobacter* enteritis, but only about 20 percent of HLA-B27-positive persons develop reactive arthritis; therefore, the absence of this marker cannot be regarded as an exclusion criterion. The bowel symptoms in inflammatory bowel disease are more prominent and tend to parallel the activity of peripheral arthritis. Gonococcal and postvenereal arthritis can be distinguished by identifying the concurrent *Neisseria gonorrhoeae* or *Chlamydia* infection by the use of DNA probe techniques and, especially in case of concurrent *Chlamydia trachomatis* infection, the exclusion of extra-articular manifestations.

Rheumatic fever and other forms of oligoarthritis can be recognized by their serological markers, such as antistreptolysin-O and antideoxyribonuclease titers. Psoriatic arthritis can be difficult to differentiate from Reiter syndrome, and careful history-taking regarding urethritis and bowel symptoms is important. The hyperkeratotic lesions in Reiter syndrome (keratoderma blennorrhagicum) appear to be indistinguishable from pustular psoriasis, but unlike in psoriatic arthritis their presence does not correlate with the course of the disease.

In all instances the diagnosis of Reiter syndrome is made after a thorough history-taking, identification of triggering enteropathogenic bacteria, and evidence of clinical and extra-articular features.

There can be unusual neurological complications. Among these complications, peripheral neuropathy, neuritis of the shoulder girdle, transient hemiplegia, meningoencephalitis, and cranial nerve lesions have been reported. In an extensive retrospective literature review, Good described the case histories of 11 patients with neuropsychiatric signs that included episodes more or less characteristic of seizure states. Two of these patients suffered from seizures that antedated the first signs of Reiter syndrome; 6 had disturbances during the acute phase variously described as obtunded, amnesic, and syncopal. Three others had psychosis during the acute phase, two of which were termed schizophrenic. In all of these cases there was no electroencephalographic evidence of seizure activity, but the documentation was inconsistent and largely anecdotal.

Central nervous system events, ranging from mild cognitive dysfunction to seizures of any type in the setting of acute arthritis, are known to occur in active systemic lupus erythematosus; most patients are women, usually of childbearing age.

In 1903 a case of postdysenteric limb paralysis was described associated with the exotoxin of *Shigella dysenteriae* I and called Shiga neurotoxin. Keusch and Jacewicz and McIver, et al. postulated the neurotoxicity of *Shigella* enterotoxins in animal experiments, and the increased rate of shigellosis associated with convulsions (12-45 percent) in children suggests the potential
neurotoxicity of those enterotoxins in susceptible individuals.

This case suggests that a functional seizure reflecting an acute illness would be a complication of Reiter syndrome. Further observation of this association seems warranted.

References