

# Cerebral Vasculitis in an Adolescent With Juvenile Rheumatoid Arthritis

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**A 16-year-old girl with longstanding polyarticular juvenile rheumatoid arthritis was referred from Chuuk State, Federated States of Micronesia, for evaluation and management of weakness and joint pains. She had a right hemiparesis with central facial weakness, polyarticular arthritis, and a dense cataract of the left eye with phthisis bulbi. Extensive evaluation using magnetic resonance angiography revealed vasculitis of the anterior and middle cerebral arteries. She was treated with "pulse" doses of methylprednisolone intravenously and she improved remarkably. Repeat angiography demonstrated dramatic improvement of the vasculitis. There is a paucity of literature regarding cerebral vasculitis in juvenile rheumatoid arthritis. That literature is reviewed, and our patient is discussed with regard to the few published reports. © 1998 by Elsevier Science Inc. All rights reserved.**

Pedersen RC, Person DA. Cerebral vasculitis in an adolescent with juvenile rheumatoid arthritis. *Pediatr Neurol* 1998;19:69-73.

## Introduction

The immunopathogenesis of the rheumatic or connective tissue diseases of childhood is poorly understood. Certainly the term *collagen vascular* to denote these conditions is passé and should no longer be used. There is little evidence that collagen is pivotal to any of these conditions with the possible exception of scleroderma. Conversely, vasculitis is a prominent feature of most. This

is especially the case with systemic lupus erythematosus (SLE), polyarteritis nodosa, dermatomyositis, and systemic juvenile rheumatoid arthritis (JRA) [1]. Classic or definite rheumatoid arthritis (RA) in adults is said to be complicated by systemic vasculitis in up to 3% of patients and is known as *rheumatoid polyarteritis*. The development of circulating immune complexes has been documented in such patients [2].

Cerebral vasculitis is distinctly uncommon in children as an isolated entity. It is rare in children or teenagers with JRA [3]. Very few cases of stroke have been reported in children with JRA [4]. We report the case of a 16-year-old Chuukese girl who developed a stroke after a 5- to 6-year history of polyarticular JRA. Her case is of special interest because her central nervous system (CNS) disease could not be attributed to medication toxicity, because she was from such a remote island that medical care was not available. We were able to study her relatively acutely and were able to document vasculitis of the arterial system of the Circle of Willis by magnetic resonance (MR) angiography. Furthermore, after aggressive medical therapy, these lesions resolved. Clinical improvement paralleled the imaging studies.

## Case Report

A 16-year-old girl was referred from Chuuk State, Federated States of Micronesia, for evaluation of weakness and joint pains. She had a 6-year history of recurrent joint pain and swelling, initially involving the right knee but eventually involving both knees, as well as ankles, elbows, shoulders, and wrists. She also complained of recurrent back pain, without a change in bowel or bladder function. Her joint discomfort progressively increased to the point where she had difficulty ambulating. Several weeks before admission, she noted right arm and leg weakness with some associated sensory changes, and she was unable to walk. She did not report any rashes, trauma, or headaches but had intermittent low-grade fevers over the past year. She had a history of recurrent bilateral iritis and a cataract of the left eye. Her family history was negative for rheumatic disease, tuberculosis, or other chronic disease. Indomethacin had recently been prescribed on an "as needed" basis for her arthritis. Her articular examination was abnormal with pain on motion and limitation of motion of the involved joints. She was unable to walk. She had no rashes, organomegaly, or heart murmurs. She was blind in the left eye, with an obvious dense cataract and atrophy of the globe. Her neurologic examination was significant for a right hemiparesis with a central facial palsy. Reflexes were brisk, more so on the right. Mild atrophy of the muscles of the right forearm and hand was noted.

Radiography revealed juxta-articular osteopenia in the bones surrounding the clinically affected joints. Whole-body scintigraphy using <sup>99m</sup>Tc demonstrated increased uptake of the right shoulder, elbow, and wrist and

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Figure 1. Whole-body bone scintigram demonstrates increased uptake of the right shoulder, elbow, and wrist and bilateral sacroiliac, knee, and ankle joints.

bilateral sacroiliac, knee, and ankle joints (Fig 1). Cranial magnetic resonance imaging (MRI) with and without gadolinium and an MR angiogram were performed. Her left globe was small and crenated in appearance, suggestive of phthisis bulbi (Fig 2). No infarcts were appreciated; however, the angiogram demonstrated beading and decreased caliber of the vessels of the Circle of Willis, involving both anterior cerebral and middle cerebral arteries (Fig 3A).

Her initial erythrocyte sedimentation rate was 124 mm/hour. Other laboratory studies included a complete blood count, which was remarkable for leukocytes of  $16,100 \times 10^9/L$  (71% neutrophils, 20% lymphocytes, 5% monocytes, and 4% eosinophils), hemoglobin of 7.0 g/dL, hematocrit of 23.3%, and platelets of  $936,000 \times 10^9/L$ . Her blood chemistries were normal or slightly elevated with a marked elevation of total protein (11 g/dL). Urinalysis was normal. Some specialized rheumatologic tests were abnormal as shown in Table 1. Cerebrospinal fluid, obtained on admission, was normal (protein, 14 mg/dL; glucose, 52 mg/dL; 1 erythrocyte; gram stain, negative; and culture, negative). Infectious disease serologies are listed in Table 2.

She was treated with methylprednisolone 1 gm intravenously over 1 hour each day for 3 days and continued her oral nonsteroidal medication, naproxen. Her pain significantly lessened, and she was able to walk with minimal assistance. Her right facial weakness and hemiparesis also dramatically improved, with only minimal residual weakness on the right. Repeat MR angiogram, performed 1 week after admission, showed improved vessel caliber on MRI (Fig 3B). An area of enhancement in the posterior limb of the left internal capsule was now seen, suggestive of an infarct. She was started on oral methotrexate, prednisone, and aspirin as an outpatient and returned to her home markedly improved.

## Discussion

Rheumatoid polyarteritis is a recognized, albeit infrequent complication of definite or classic RA. Stroke is a frequent concomitant of polyarteritis, and immune complexes (presumably containing rheumatoid factors and complement) are thought to be pathogenic. Clinically, CNS disease is relatively common in a number of systemic connective tissue diseases of childhood, notably SLE where CNS manifestations are included as a major criteria for diagnosis [5]. Headaches, seizures, depression, diplopia, organic brain syndrome, and a variety of other neuropsychiatric signs and symptoms have been reported [6]. Interestingly, even in childhood lupus CNS disease, strokes have rarely been reported.

There is little evidence of CNS disease in JRA, with the possible exception of systemic JRA (Still's disease) in which multiple organ systems, including the CNS, may be affected [3]. The hallmarks of systemic JRA include polyarthritis, high-spiking fever (higher than  $39.5^\circ\text{C}$ ), an evanescent salmon-pink rash, polyserositis, and characteristic but nonspecific laboratory abnormalities, such as leukocytosis, hemolytic anemia, and thrombocytosis. Abnormal blood chemistries are thought to be a reflection of the underlying disease, as are toxic effects of the various medications used to treat life-threatening systemic JRA. Certainly, young children with systemic JRA may be quite irritable, suggesting meningeal irritation similar to that seen commonly in Kawasaki disease. With longstanding JRA, the cervical spine is often inflamed, rarely resulting

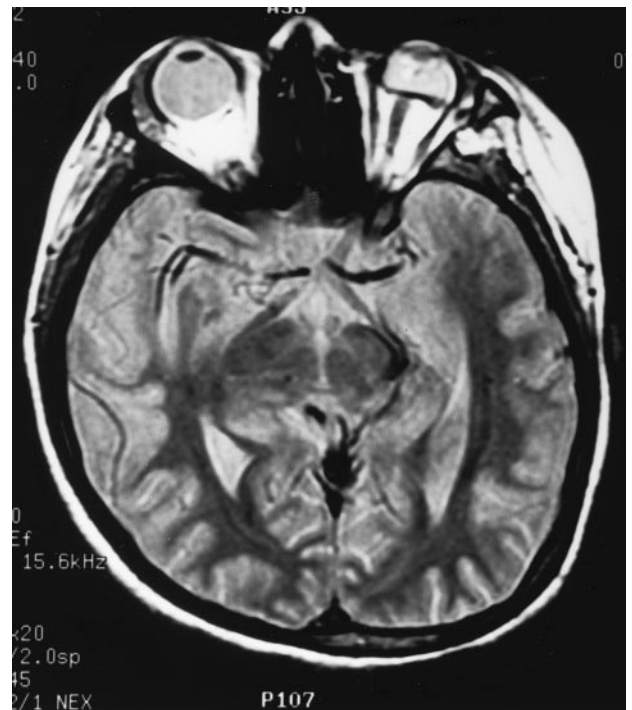
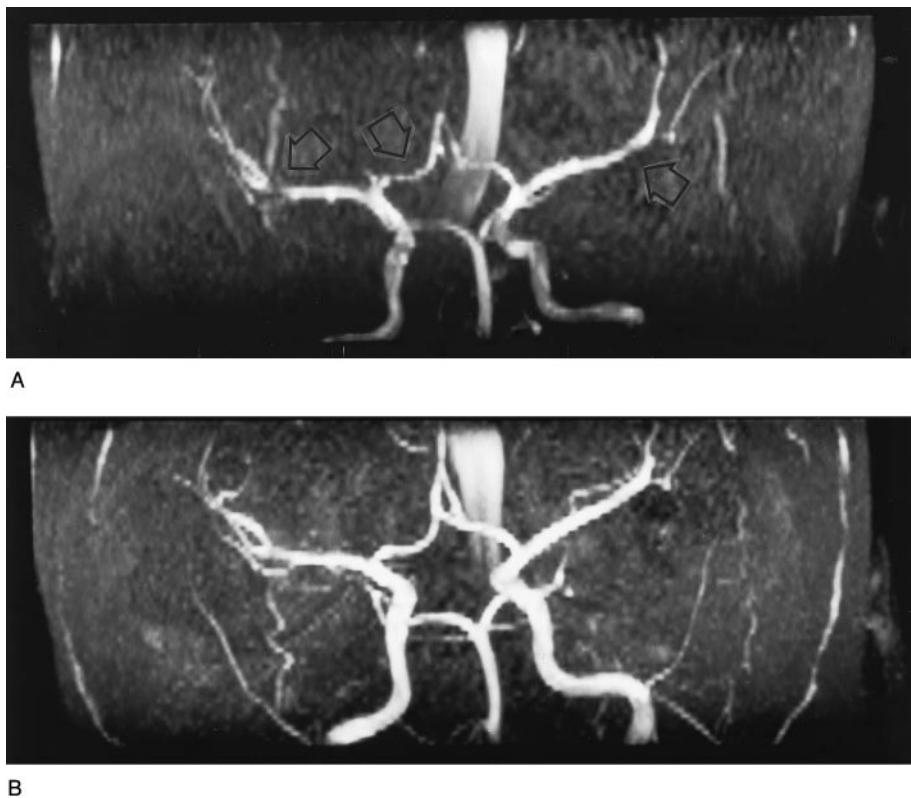


Figure 2. Proton density weighted (TR: 3,300 ms; TE: 16 ms) magnetic resonance imaging of the brain demonstrates crenated appearance and abnormal signal of the left globe (phthisis bulbi).

Figure 3. (A) Magnetic resonance angiogram demonstrates narrowing of the distal branches of the anterior and middle cerebral arteries (arrows). (B) Magnetic resonance angiogram 1 week after pulse steroid therapy demonstrates improved vascular caliber of the anterior and middle cerebral arteries.



in wry neck. One of us (D.A.P.) has followed several such children and children with JRA and seizures, but these cases are unusual. The critically ill child with life-threatening systemic JRA may manifest evidence of hypertensive encephalopathy thought to be secondary to long-term high-dose corticosteroids [3]. Still others succumb to

bacterial or fungal meningitis, again because of the immunosuppression of high-dose corticosteroids and cytotoxic drugs, which are commonly used to treat this form of the disease.

A recent comprehensive review of CNS vasculitis failed to mention JRA as a cause of CNS vasculitis [7]. Steiner and Gelbloom [8] reported two patients with RA who developed meningeal granulomas and necrotizing arteritis of the cerebral vessels. Both were adult men, aged 32 and 62 years, with longstanding, progressive, deforming, nodular polyarticular RA. Both very likely had circulating antiglobulins (rheumatoid factor [RF]), but their report antedated routine testing for RF [9], and both patients had been treated with cortisone. The former developed RA at the age of 16 years and thus would have been considered

Table 1. Immunologic tests

Test	Result (Control)
ANA	Negative (negative)
RF	<20.0 (<20.0 IU/mL)
IgG, IgM, IgA	4,680, 335, 924, (694-1,618, 60-263, 69-309 mg/dL)
C3, C4, CH 50	253, 29, 240 (86-185, 19-59, 60-144 mg/dL)
ANCA	<1:16 (<1:16)
Anticardiolipin IgG, IgM	7, 11 (<11GPL, <11MPL)
HLA-B27	Positive (negative)
Raji cell assay	7 (0-16 $\mu$ gE/mL)
Complement 1q binding activity	18 (0-19.9 $\mu$ gE/mL)
Coombs (D/I)	Negative/negative (negative/negative)

Abbreviations:

- ANA = Antinuclear antibody
- ANCA = Antinuclear cytoplasmic antibody
- C = Complement
- CH 50 = Total hemolytic complement
- D/I = Direct/indirect
- HLA-B27 = Human leukocyte antigen B-27
- Ig = Immunoglobulin
- RF = Rheumatoid factor

Table 2. Serology

Test	Result	(Control)
HB <sub>s</sub> Ag	Negative	(Negative)
HB <sub>s</sub> Ab	NR	(NR)
ASO	2,090	(<250 IU/mL)
Antihyaluronidase	1:1,024	(<1:256)
Anti-DNase B	1:680	(<1:170)

Abbreviations:

- ASO = Antistreptolysin O
- HB<sub>s</sub>Ag = Hepatitis B surface antigen
- HB<sub>s</sub>Ab = Hepatitis B surface antibody
- NR = No response

to have met the criteria for a diagnosis of JRA. Sievers et al. [10] reported the case of a 17-year-old boy with JRA of several years' duration who developed focal neurologic signs and symptoms. Initially thought to be secondary to a brain tumor, it was subsequently shown by angiography to be due to cerebral vasculitis, which resolved with corticosteroid. They described three children in detail, all boys, ages 2 years, 6 months; 4 years; and 4 years, 6 months, all of whom developed seizures. From their descriptions, all three had systemic JRA and were being treated with high doses of acetosalicylic acid (120 mg/kg). The second boy developed hepatic toxicity with hepatic encephalopathy 10 days after halothane anesthesia for dental extractions. He died 2 months later. Russell took exception with these authors' interpretation and suggested aspirin or corticosteroid toxicity as a possible cause of the CNS disease [11]. Sillanpaa et al. [12] described a 15-year-old boy with JRA who died of cerebral edema after right hemiparesis and disturbed speech and swallowing. Postmortem examination revealed intravascular and perivascular mononuclear cell infiltrates, presumptive evidence of intracerebral vasculitis. Gururaj et al. [4] described a 5-year-old girl with JRA and partial motor seizures. After a left-sided clonic seizure that was preceded by a visual hallucination, she developed transient left hemiparesis. The initial computed tomography revealed an area of enhancement of the right occipital lobe, which the authors suggest represented an area of infarction. No further imaging was performed, and her neurologic recovery was "rapid." Focal abnormalities on computed tomography have been reported after a seizure, probably representing edema resulting from a transient change in blood-brain barrier permeability [13]. The patient described here more likely represents an example of transient radiographic and neurologic deficits after a seizure, or Todd phenomenon, and not an infarct resulting from JRA and vasculitis. Jan et al. retrospectively reviewed the medical records of 170 patients with JRA, 13 of whom had signs of CNS dysfunction [14]. None had symptoms suggestive of cerebral infarction.

Our patient is unique in a number of respects. Her home is a remote, outer island in Chuuk State (formerly Truk) in the Western Pacific, one of the Federated States of Micronesia. There was nothing unusual about her birth, growth and development, early school years, or family history. She neither sought nor was there available any more than the most basic of medical care. She was said to have had recurrent bouts of symmetric polyarthritis, inactivity stiffness, back pain, and bilateral inflammatory eye disease for the past 5 or 6 years. These episodes would resolve spontaneously without treatment, although she developed a cataract and was blind in the left eye. Recurrent polyarthritis in a Pacific Islander would be almost pathognomonic for recurrent acute rheumatic fever (ARF), and indeed she had serologic evidence for a recent streptococcal infection. However, she had no clinical or echocardiographic evidence of valvular heart disease, and she did not have Sydenham chorea or any other of the

major manifestations of ARF, namely, subcutaneous nodules and erythema marginatum. Recurrent iritis is a well-recognized concomitant of JRA, particularly in antinuclear antibody (ANA) positive little girls with pauciarticular (four or fewer joints) JRA. Iritis, however, has been observed occasionally in polyarticular and systemic JRA patients. Recurrent uveitis, usually symptomatic, has been reported in patients with seronegative spondyloarthropathies (e.g., ankylosing spondylitis, inflammatory bowel disease, Reiter syndrome). These conditions are highly associated with the histocompatibility antigen, HLA-B27, coded for at the major histocompatibility locus on the short arm of chromosome 6, and are present in our patient. The seronegative spondyloarthropathies are significantly more common in males than females by a ratio of 10:1, and CNS disease is distinctly unusual. Our patient's ophthalmologic examination was more suggestive of recurrent iritis of JRA than that seen in chronic seronegative spondyloarthritis.

Systemic vasculitis could easily result in a stroke; however, our patient lacked the commonly associated serologic markers, namely, ANA, hepatitis B surface antigen, antinuclear cytoplasmic antibody, and anticardiolipin antibodies and evidence of circulating immune complexes (negative Raji cell and Clq binding assays) and elevated rather than depressed complement levels.

With the exception of polyarthritis and CNS disease, she does not fulfill the criteria for a diagnosis of SLE, and her ANA and anti-DNA antibody tests were negative. Likewise, she does not fulfill the criteria for a diagnosis of systemic JRA. She does not have ARF, and iatrogenic or drug-induced CNS disease is excluded by virtue of the fact that she did not have access to health care before her evacuation to our facility. The patient reported here has seronegative (i.e., RF negative) polyarticular JRA.

MR angiography revealed cerebral arteritis consistent with her clinical stroke syndrome, and aggressive medical treatment resulted in resolution of her CNS disease, improvement of her JRA, and angiographic evidence of improved flow in the Circle of Willis. Although infrequent, JRA should be considered as etiology for CNS vasculitis and stroke in the young.

**Note added in proof:** On February 18, 1998 the patient was examined at Chuuk State Hospital and found to be in complete remission.

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