

## NEUROLOGICAL BULLETIN

FEATURING ARTICLES BY TRAINEES IN NEUROLOGY & NEUROSCIENCE

### **Adult-Onset Still's Disease with Parkinsonian Features**

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#### Introduction

Adult-Onset Still's Disease (AOSD) is a systemic inflammatory rheumatologic disorder characterized by some or all of the following features: fever of unknown origin, an evanescent maculopapular rash, arthritis or arthralgias, pharyngitis, hepatosplenomegaly, lymphadenopathy, and serositis. The pathophysiological basis of AOSD has yet to be described. This rare disease has been associated occasionally with central and peripheral nervous system involvement and with focal changes on cranial magnetic resonance imaging. In this case report, we describe a new clinical profile of AOSD with parkinsonian manifestations.

AOSD is a rare entity, with an estimated prevalence of less than 1 case in 100,000 people. AOSD is a common cause of fever of unknown origin (FUO). Co-infections at the time of diagnosis include cytomegalovirus, Epstein-Barr virus, human herpes virus type 6, coxsackie virus, mumps, rubella, human immunodeficiency virus, echovirus, par-

vovirus B19, Hepatitis virus types A, B, and C, Chlamydia pneumonia, Mycoplasma pneumonia, and Campylobacter jejuni, and yet AOSD remains a diagnosis of exclusion. All sources of FUO related to diverse causes such as infection, neoplasm, and autoimmune diseases (e.g. endocarditis, lymphoma, vasculitides, or polymyositis) must all be considered and excluded before AOSD is diagnosed.<sup>1</sup>

Neurological involvement occurs infrequently with AOSD and includes cognitive impairment, transient pyramidal tract symptoms, peripheral neuropathy, and aseptic meningitis.<sup>2</sup> We report a case of AOSD with parkinsonian manifestations and thought it would be important and valuable to add this to the published spectrum of neurological involvement.

#### History of Present Illness

A 35-year-old African-American woman with no significant past medical history presented to our hospital with the chief com-

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plaints of persistent fevers, chills, and generalized lethargy for 2 weeks. Just prior to this hospitalization, she noticed an erythematous swollen area on her right lower extremity that she initially presumed to be an insect bite. She was taken to a local hospital with the erythematous area now progressing into a rash that was associated with fever of 105°F, chills, and generalized lethargy. On admission to the outside hospital, she was noted to have a macular non-pruritic rash on the extensor surfaces of elbows, symmetric polyarthralgias, fatigue, nausea, vomiting, and diarrhea. This was thought to be a viral syndrome and was treated with ibuprofen. Her symptoms persisted for 4 days with worsening leukocytosis (19,000 WBC/ $\mu$ L). She was started on intravenous vancomycin, ceftriaxone, and metronidazole for likely treatment of sepsis.

When her condition failed to improve over the next 5 days, she was transferred to our hospital for further evaluation. On presentation, she provided a constellation of symptoms including sinus congestion, headache, cough with blood-tinged mucous, dyspnea with exertion, watery diarrhea, and non-bilious, non-bloody, clear emesis. She denied neck stiffness, weakness, confusion, or loss of sensation. She had a diffuse erythematous blanching non-pruritic plaque-like rash with a malar distribution. She also complained of a bilateral arm trembling when she tried to use her hands. This was the first time she had ever had a tremor.

On admission, her laboratory evaluation was notable for leukocytosis with 33.6% neutrophilic bands (normal 0-7%) and transaminitis (ALT 62 U/L (normal <55 U/L); AST 132 U/L (normal <35 U/L)). Monospot, human chorionic gonadotropin, *Clostridium difficile*, and hepatitis panel were negative. She was initially continued on vancomycin and piperacillin/tazobactam. With fevers persist-

ing, doxycycline was added for presumed tick borne illness. Over the next 4 days, her fevers continued in spite of broad spectrum antibiotics and a decision was made to discontinue antibiotics. Additionally, blood and urine cultures failed to grow any organisms. An evaluation for rheumatologic disorders was initiated but tests for systemic lupus erythematosus, rheumatoid arthritis, and mixed connective tissue disease were negative. Notably, anti-double-stranded DNA antibody <1 IU/ml (normal <5.0 IU/ml), anti-ribosomal P, anti-centromere, anti-Smith, anti-RO, anti-LA, anti-JO-1, anti-SCL-70, anti-chromatin IgG, Anti-Smith Ag Ribonuclear Protein, anti-myeloperoxidase, and anti-proteinase 3 antibodies were all <0.2 AI (normal <1.0 AI). The lone positive rheumatologic antibody was anti-ribonucleoprotein (anti-RNP), which was 2.7 AI (normal < 1.0 AI). Elevations in other acute phase serological markers were noted; Erythrocyte Sedimentation Rate (38 mm/hr) (normal 0-20 mm/hr), C-reactive protein (35 mg/dL) (normal <0.9 mg/dL), ferritin (>40,000 ng/mL) (normal 5-200 ng/mL), and lactate dehydrogenase (LDH) of (1100 U/L) (normal 180-360 U/L). Complement panels and anti-myeloperoxidase antibodies were negative. Titers for Ehrlichia, Lyme disease, Rocky Mountain spotted fever, cytomegalovirus, and Epstein-Barr virus were negative.

At this point, a provisional diagnosis of AOSD was made and she was started on treatment with intravenous dexamethasone at 4 milligrams twice daily. Within 12 hours of initiation of steroid therapy, we noted resolution of fever, arthralgias and myalgias. Interestingly, it was at this time that she noticed a worsening in her resting tremor. On neurological evaluation she was found to be alert and oriented to person, place, and time. Conversation revealed slight masked facies and hypophonia. There was a mild lingual tremor noted but the remainder of her cranial

nerve exam was normal. Her muscle strength was full, but she had increased tone with cogwheel rigidity. Hyperreflexia with spread was present in her upper extremities and there was clonus at her ankles. Her movements were bradykinetic and rapid alternating movements were clumsy. Her gait was unsteady. In summary, she demonstrated all four of the cardinal Parkinsonian features including bradykinesia, resting tremor, rigidity and postural instability. Review of her chart and history confirmed no family history of Parkinson's disease. Throughout the course of her illness, she was never given any dopaminergic antagonists such as metoclopramide, nor was she given any antidepressant medications that could cause drug induced parkinsonism. Cranial MRI without and with contrast was unremarkable. Over the next week, her rash, myalgias, and arthralgias improved as her fevers resolved. Her Parkinsonian features persisted unchanged however, even as her systemic signs and symptoms resolved. With her overall clinical condition improving, she was discharged to home with a plan for follow up with the neurology and rheumatology clinics.

At a follow-up rheumatology appointment 25 days after discharge, she was afebrile and had no neurologic complaints. Other than a slight, low-amplitude 6 Hz intention tremor on finger-to-nose testing, her exam had returned to normal with no evidence of Parkinsonism including resolution of her bradykinesia, resting tremor, rigidity, and postural instability. A plan was made to taper her steroids over two weeks. After cessation of steroid therapy, she reported nightly fevers to 102°F that responded well to ibuprofen but interestingly, did not have recurrence of her neurologic symptoms. Follow up four months after her hospitalization revealed that she continues to take nightly ibuprofen and has not had to be restarted on corticosteroids.

## Discussion

In 1897, George Frederic Still described a form of rheumatoid arthritis that presented in childhood with polyarthralgias, lymphadenopathy, splenomegaly, hyperhidrosis and a characteristic salmon-pink rash.<sup>3</sup> There is currently debate about the distinction of systemic onset juvenile rheumatoid arthritis (JRA, formerly known as Still's Disease) as a unique entity in the spectrum of JRA. Systemic onset JRA is a diagnosis of exclusion in patients younger than 16 years of age. Certain characteristic laboratory findings are associated with systemic onset JRA: WBC count >20,000/ $\mu$ L (sometimes up to >80,000/ $\mu$ L) with granulocyte predominance, reactive thrombocytosis, iron deficiency anemia, elevated ESR (sometimes >100 mm/hr), minor elevations of AST/ALT, hypoalbuminemia and hyperglobulinemia.<sup>4</sup>

A condition with similar characteristics was later noted in the adult population.<sup>5</sup> Adult-Onset Still's Disease is a systemic inflammatory rheumatologic disorder characterized by daily fevers, an evanescent rash, and arthralgias. The clinical presentation of AOSD is variable. Most patients present with fever, pharyngitis, polyarthralgias, arthritis and/or rash. Fever is usually greater than 39°C, starts abruptly and may be the only presenting symptom. Two of three patients present with arthralgias, which can occur at any joint and typically accompany fever onset. A migratory arthralgia is noted at presentation and becomes more stable at certain joints during the latter part of the illness. A transient skin rash is considered characteristic of the disease, usually macular or maculopapular, salmon-colored and non-pruritic.<sup>1</sup>

Unfortunately, AOSD remains a diagnosis of exclusion with a wide differential and an absence of 100% specific diagnostic criteria. Several groups have published criteria based

on retrospective data, but the Yamaguchi criteria appear to have the greatest sensitivity and specificity for identifying AOSD. Our patient met the Yamaguchi criteria for AOSD with a 2 week history of arthralgias, a leukocytosis of greater than 10,000 WBC/ $\mu$ L, a maculopapular rash on the trunk during febrile episodes, pharyngitis, lymphadenopathy, abnormal liver function tests, negative antinuclear and rheumatoid factor antibody screen, elevated ESR and a hyperferritinemia of greater than 40,000 ng/mL. Because our patient met more than 5 of the Yamaguchi criteria, including more than 2 major criteria, the sensitivity of diagnosis is 96.2% and specificity is 92.1%.<sup>6</sup>

Other systemic manifestations of AOSD that are well-documented include myocarditis, respiratory insufficiency, bone marrow failure, anemia, glomerulonephritis, acute renal failure, destructive arthritis, and retro-orbital myositis.<sup>7</sup>

On rare occasions, the disease also affects the central or peripheral nervous system. Central nervous system involvement may occur in 7-12% of cases.<sup>8,9</sup> The most common presentation is aseptic meningitis, but it is unclear if the relationship is causal.<sup>2,10</sup> Mechanisms speculated for CNS involvement include meningeal inflammation as part of a systemic inflammatory response or activated neutrophils penetrating a compromised blood brain barrier inducing meningitis, and or undetected bacterial inflammation.<sup>10</sup>

More restricted and focal central nervous system involvement has been described less often. Shimohata, et al reported AOSD with ataxia and left abducens palsy and T2 hyperintensities on MRI in the left abducens nucleus, left inferior cerebellar peduncle, and right anteromedial thalamus, which correlated with the patient's clinical symptoms. Interestingly, our patient previously had sensorineural hearing loss which improved clinical-

ly with corticosteroid treatment.<sup>11</sup>

The Parkinsonian signs we observed seem not to have been previously described in the literature with AOSD and remarkably, her MRI was normal. Her tremors initially worsened after corticosteroid administration but with continued treatment all of her neurological manifestations resolved without the need for any specific anti-parkinsonian therapy. It is our suspicion that the initial worsening was likely coincidental.

In summary, we present a case of a 35-year-old African-American woman who developed new-onset Parkinsonian tremor, rigidity, and bradykinesia during the course of a new-onset of Adult-Onset Still's Disease. Given the limited data available regarding the neurological manifestations, we hope to draw attention to a novel and significantly disabling presentation of this rare systemic inflammatory disease.

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