

Autoantibody to Signal Recognition Particle in African American Girls with Juvenile Polymyositis

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ABSTRACT. Anti-signal recognition particle (anti-SRP) is a myositis-specific autoantibody that is linked to a severe polymyositis (PM) associated with interstitial lung disease (ILD) and esophageal dysmotility in adults. We describe 3 African American adolescent girls with anti-SRP juvenile PM. One child required aggressive treatment to control her disease and 2 were refractory to multiple immunosuppressants. Patient 1 developed ILD and cardiac disease; Patient 2 developed ILD; Patient 3 developed esophageal dysmotility and cardiac disease. Organ system involvement was comparable to that seen in adults. We conclude that testing for anti-SRP in children with PM may facilitate diagnosis and management. (First Release Mar 1 2008; J Rheumatol 2008;35:927–9)

Key Indexing Terms:

JUVENILE POLYMYOSITIS ANTI-SIGNAL RECOGNITION PARTICLE AUTOANTIBODY

Idiopathic inflammatory myopathies (IIM) are a group of disorders characterized by proximal muscle weakness and serum muscle enzyme elevation. While juvenile dermatomyositis (JDM) is the most common pediatric inflammatory myopathy, with an annual incidence of 3.2 per million children¹, the incidence of juvenile polymyositis (JPM) is unknown, but much rarer than JDM. Autoantibodies have been described in IIM and are divided into “myositis-specific autoantibodies” (MSA), occurring almost exclusively in patients with myositis, and “myositis-associated autoantibodies” (MAA), occurring in patients with autoimmune diseases that have a myositis component.

Autoantibody to the signal recognition particle (anti-SRP) is a MSA. The SRP complex is a ubiquitous cytoplasmic ribonuclear protein consisting of a small 7S RNA associated with 6 proteins of molecular weights 9, 14, 19, 54, 68, and 72 kDa, which transport proteins to the endoplasmic reticulum². In adults, anti-SRP is associated with a severe PM often resistant to immunosuppressive therapy^{3–9}. To our knowledge, only 4 children with anti-SRP JPM have been reported^{4,10}.

From 1996 to 2006 the Immunology/Rheumatology Clinic at Children’s Memorial Hospital, Chicago, tested 123 children with myositis for MSA/MAA by immunoprecipitation (INT, University of Oklahoma) as described³, and 3 (2%) tested positive for antibodies to SRP. In contrast, studies in adults have suggested that 4%–6% of patients with PM or DM have anti-SRP^{4–7,11}. We describe 3 children with anti-SRP JPM, all African American girls presenting during adolescence.

CASE REPORTS

Patient 1 was a 16-year-old African American girl who was well until February 1999, when she developed upper arm weakness. She had a flu-like illness 2 weeks prior and reported color changes in her hands consistent with Raynaud’s. Her weakness rapidly progressed; in March 1999 she was hospitalized. On examination, she had extreme weakness of upper/lower extremities and neck flexors and wrist arthritis; remaining examination was unremarkable. Creatine kinase (CK) was 22,155 IU/l; muscle biopsy demonstrated degeneration and necrosis of muscle fibers invaded by lymphocytes. Despite oral prednisone 60 mg daily and methotrexate (MTX) 25 mg subcutaneous weekly, weakness persisted. She was referred to Children’s Memorial Hospital in May 1999. CK had decreased to 3534 IU/l, but she had profound weakness on examination, with extensive changes seen on magnetic resonance imaging (MRI). MSA/MAA testing was positive for anti-SRP; other autoantibodies were negative. Pulmonary function test revealed mild lung restriction with impaired diffusing capacity (DLCO 64% of predicted); high resolution chest computerized tomography (CT) showed honeycombing at both bases. Echocardiogram demonstrated left ventricular hypertrophy. Barium swallow was unremarkable. Medications included intravenous (IV) methylprednisolone 1 g 3 times/week with oral prednisone 30 mg (0.35 mg/kg) on other days, hydroxychloroquine 400 mg daily, and monthly IV cyclophosphamide (500–750 mg/m² for 6 mo). In October 1999, she developed ovarian failure; cyclophosphamide was discontinued and tacrolimus 7 mg twice/day (0.2 mg/kg/day) was initiated. Subsequently, she developed hemolytic uremic syndrome; tacrolimus was discontinued and mycophenolate mofetil (MMF) 1000 mg twice/day (25 mg/kg/day) was started. Kidney function returned to normal and she has not developed further renal sequelae.

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lae. Her weakness improved modestly until June 2002, when she was unable to lift her arms, legs, or head immediately following a respiratory infection. Infliximab 4 mg/kg was started in August 2002 and by January 2003 infusions were stopped as she had no improvement. Currently, she uses a wheelchair, but despite this is attending college.

Patient 2 was a 14-year-old African American girl who was well until December 2000, when she developed sinusitis in association with lower extremity weakness. Her weakness progressed to involve the arms and in January 2001 she was hospitalized. Examination demonstrated 1/5 proximal muscle and 3/5 distal muscle weakness of upper and lower extremities and wrist arthritis; remaining examination was unremarkable. CK was 22,857 IU/l and muscle biopsy demonstrated a necrotizing myopathy without inflammation. She received IV gammaglobulin (IVIG) 1 g/kg and oral prednisone 80 mg (1 mg/kg) daily. CK had decreased to 1189 IU/l; weakness improved slightly. In May 2001 oral MTX 15 mg (7 mg/m²) weekly was started and later increased to 25 mg (12.5 mg/m²) weekly. In July 2001, she developed sinusitis and CK increased to 11,151 IU/l. MMF 1000 mg twice/day (23 mg/kg/day) and IVIG 1 g/kg monthly was started, with minimal improvement in weakness. In April 2002 monthly IV cyclophosphamide (500–750 mg/m²) was administered for 6 months. By July 2002, she had only slight improvement in weakness and infliximab 3 mg/kg was administered. She presented to Children's Memorial Hospital in August 2002 for a second opinion. CK was 2975 IU/l and examination showed extraordinary weakness. MSA/MAA testing was positive for anti-SRP; other autoantibodies were negative. IV methylprednisolone 1 g weekly and prednisone 0.5 mg/kg/day was started. Pulmonary function demonstrated DLCO 75% of predicted; chest CT showed linear opacities at the bases suggestive of an inflammatory process. Echocardiogram, electrocardiogram, and barium swallow were unremarkable. She started taking cyclosporine 1.2 mg/kg twice/day and IV methylprednisolone was administered twice/week. Despite normalization of her CK, she continues with 1/5 weakness in her extremities and neck flexors and currently uses a wheelchair.

Patient 3 was an 11-year-old African American girl who was well until January 2001, when she developed weakness in proximal upper and lower extremities preceded by a viral respiratory infection. Weakness progressed and in June 2001 she was hospitalized. On examination, she had 1/5 weakness in upper and lower extremities; remaining examination was unremarkable. Her CK was 33,000 IU/l and muscle biopsy demonstrated myofiber necrosis with interstitial and perivascular infiltration. Oral prednisone 100 mg daily (2 mg/kg) was initiated. By September 2001 CK had decreased to 2384 IU/l; clinically she remained weak and barium swallow demonstrated poor motility in the proximal esophagus. Oral MTX 20 mg/m² weekly and IVIG monthly were started. In February 2002, infliximab 3.5 mg/kg was begun in an attempt to taper prednisone. Her weakness progressed, while CK increased to 1055 IU/l. Cyclosporine 2 mg/kg twice/day was started in September. She was gradually improving until February 2003, when she developed influenza. She developed Raynaud's. CK increased to 1060 IU/l. Cyclosporine was discontinued; azathioprine 3 mg/kg daily was initiated. CK continued to increase and in August 2003, azathioprine was discontinued and cyclosporine 3 mg/kg twice/day was restarted. She was referred to Children's Memorial Hospital for a second opinion. Her neck flexors were 3/5 and upper and lower extremities were 4/5; she had knee synovitis.

MSA/MAA testing was positive for anti-SRP; other autoantibodies were negative. An echocardiogram demonstrated left ventricular hypertrophy with normal function. Pulmonary function testing was requested, but not performed. Currently, she has mild physical limitations, as she is unable to run well, but otherwise has normal function.

DISCUSSION

Clinical features for the 3 patients are listed in Table 1. All patients presented with markedly elevated CK, similar to adults with anti-SRP⁸. Patients 1 and 2 developed profound weakness within 2 months of onset of symptoms and both are currently wheelchair-bound. Patient 3 developed severe weakness within 6 months of onset of symptoms. Patients 1 and 2 had evidence of ILD. Patient 3 had esophageal dysfunction and left ventricular hypertrophy on echocardiogram. Systemic involvement of the lungs and esophagus has been described in adults with anti-SRP⁴⁻⁹. However, most adults with anti-SRP do not develop arthritis or Raynaud's, suggesting a slightly different phenotype in pediatric patients. Love, *et al* initially reported cardiac disease in adult anti-SRP patients⁴, which was documented in 2 of our patients. Subsequent reports in adults have not found significant cardiac involvement^{6,9}. All 3 patients had a necrotizing pattern on muscle biopsy, which is characteristic of adult patients with anti-SRP PM⁹ and distinct from the endomysial inflammatory infiltrate seen in JDM. Despite the use of multiple immunosuppressants, all 3 patients continue to have active disease, which is similar to the data from adults with anti-SRP^{4-6,8,9}.

Interestingly, all 3 patients are female, in contrast to the nearly equal sex distribution of patients with anti-SRP with adult-onset PM^{3,6}. Of the children with JPM, 3 of 3 (100%) anti-SRP patients were African American; Love, *et al*⁴ reported 5 of 7 (71%) anti-SRP adult patients were black, while Kao, *et al*⁶ reported 5 of 14 (26%) were black. Further epidemiologic studies in children and adults with PM need to be performed to more fully understand the sex and racial distributions.

Although an etiology for IIM has failed to emerge, a seasonal pattern of disease onset in late fall to winter has been described in adults with anti-SRP PM¹². All 3 children had onset of weakness in winter months and infection preceded or coincided with this. Additionally, disease exacerbations occurred immediately following infections. This suggests the possible role of an infectious catalyst in the etiology of

Table 1. Clinical characteristics.

Patient	Age at Disease Onset, yrs	Month at Onset	Peak CPK, IU/l	Cardiac Involvement	GI Dysmotility	ILD	Arthritis	Raynaud's
1	16	Feb	22,155	+	–	+	+	+
2	14	Dec	22,857	–	–	+	+	–
3	11	Jan	33,000	+	+	NT	+	+

ILD: interstitial lung disease; NT: not tested; CPK: creatinine phosphokinase; GI: gastrointestinal.

IIM, which has been implicated in gene expression profile studies¹³ and classical epidemiology studies¹⁴.

Although associations cannot be made, it is noteworthy that of the children with myositis evaluated in our clinic, all with SRP JPM were African American girls. Our data suggest that African American girls with anti-SRP JPM exhibit a rapidly progressive myopathy with a marked elevation in CK and organ system involvement comparable to that seen in adults. Prognosis appears to be poor, and patients are refractory to immunosuppressive treatment. We conclude that testing for anti-SRP in children may facilitate diagnosis and management in patients with refractory PM.

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