Grand Rounds in Rheumatology

Miller Fisher syndrome in adult onset Still’s disease: case report and review of the literature of other neurological manifestations

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Abstract
Adult-onset Still’s disease (AOSD) is a multi-system inflammatory disorder characterized by high spiking fevers, evanescent salmon-coloured rash, arthralgias or arthritis, hepatosplenomegaly, lymphadenopathy and sore throat. There is no specific test or combination of tests that can establish the diagnosis of AOSD and patients may present with other systemic involvement including neurological manifestations in 7–12% of cases. We present a complex case of a patient with AOSD who developed the Miller-Fisher variant of Guillain–Barré syndrome. This immunological disorder of the nervous system has not been described in association with AOSD before. We also review the literature on other neurological manifestations in AOSD.

KEY WORDS: Miller Fisher syndrome, Still’s disease, Guillain–Barré syndrome, Neurological manifestations, Adult Still’s disease, gangliosides.

Introduction
Adult onset Still’s disease (AOSD) is a multi-system, inflammatory disorder characterized by high spiking fevers, evanescent salmon-coloured rash, arthralgias or arthritis, hepatosplenomegaly, lymphadenopathy and sore throat (Table 1). Patients often have a marked leucocytosis while other markers of rheumatological disorders, such as rheumatoid factor and antinuclear antibody, are negative. Other laboratory manifestations observed in AOSD include elevations in liver enzymes, abnormalities in haematological function ranging from anaemia to disseminated intravascular coagulation and markedly elevated levels of ferritin in the active stage of disease [1–4]. There is no specific test or combination of tests that can establish the diagnosis of AOSD. However, in the presence of a compatible clinical scenario, serum ferritin higher than 3200 ng/ml is highly suggestive of AOSD [5].

Almost all organ system involvement has been noted in patients with AOSD. These include pulmonary manifestations ranging from pleuritis to pneumonitis, cardiac abnormalities such as pericarditis, pericardial tamponade and myocarditis, and renal manifestations presenting as proteinuria during the febrile phase as well as microscopic haematuria and nephrotic syndrome [2]. We describe a complex case of AOSD who developed the Miller-Fisher variant of Guillain–Barré syndrome and review the literature on neurological manifestations of AOSD.

A 19 yr-old Hispanic female with an unremarkable medical history, who was 4 months pregnant, presented to the obstetrics service in late 1995 with arthralgias and a maculopapular rash during her second pregnancy. She complained of sore throat and pain and swelling in the wrists, metacarpophalangeal joints and proximal interphalangeal joints of both hands. Her elbows, shoulders, knees, and toes were involved to a lesser degree. The rash was diffuse and mildly pruritic.

On examination, she was febrile to 38°C with normal blood pressure and pulse. An erythematous maculopapular rash was evident over the forearms, thighs, abdomen and back. There was diffuse muscle tenderness but no synovitis. The remainder of her examination was unremarkable apart from the pregnancy. Her erythrocyte sedimentation rate was 103 mm/h; antinuclear antibody, rheumatoid factor and serologies for human immunodeficiency virus, rubella and Epstein–Barr virus were all negative. The titre of parvovirus B19 IgM was
positive at 1:56. She was diagnosed with acute parvovirus B19 arthritis and was treated with prednisone 10 mg daily with dramatic improvement in her aches and pains as well as rash.

Over the next 3 months, however, she continued to have intermittent arthralgias, rash and fevers. She also complained of fatigue and began losing weight during her third trimester. This as well as evidence of fetal hydrops, necessitated delivery by Caesarian section at 7 months. The baby was diagnosed with congenital cytomegalovirus infection and required prolonged admission to the intensive care unit.

Post-partum, she continued to complain of febrile episodes, arthralgias and diffuse myalgias severe enough to interfere with her ability to care for her two small children. She denied oral ulcers, alopecia, shortness of breath, pleuritic chest pain, abdominal pain, Raynaud’s phenomenon, photosensitivity, numbness, paraesthesias and focal weakness. The macular rash was apparent during febrile episodes and again involved primarily the proximal limbs and trunk. A new finding was posterior cervical and axillary lymphadenopathy. Laboratory investigations revealed haemoglobin of 7.9 g/dl, which was attributed to her recent Caesarian section as well as poor nutritional status. The white blood cell count was in the range of 13 000 mm³. Repeat parvovirus B19 IgM and IgG were negative.

Six months after her initial presentation, she was admitted for further work up of persistent arthralgias, intermittent fevers, progressive weight loss and profound anaemia, which had proven refractory to iron supplementation. This was the first of many admissions and the beginning of a very thorough and expensive evaluation. Over the course of the next 18 months, multiple investigations were undertaken, as outlined in Tables 2–4. In August 1996 she underwent a laparotomy with liver biopsy, sampling of multiple abdominal lymph nodes and repeat bone marrow biopsy. Splenectomy was performed for ‘lymphoma staging’ and possible idiopathic thrombocytopenic purpura as her platelets dropped as low as 20 000 mm³. Serum and urine protein electrophoresis was non-specific and did not suggest a monoclonal gammopathy. The liver biopsy and histopathology of lymph nodes and spleen did not show evidence of lymphoma. She developed a leucocytosis in the range of 20 000–49 000 cells/mm³ and her serum ferritin levels were noted to be markedly elevated, to between 2400 and 9850 ng/ml (normal value 16–400 ng/ml).

A diagnosis of AOSD was made (Table 1). In addition to diagnostic criteria, supportive features included the high serum ferritin concentration and wrist radiographs showing non-erosive bony fusion of the carpal bones (Fig. 1).

She was treated initially with non-steroidal anti-inflammatory drugs and then with prednisone at doses of 10–20 mg/day, though doses in the range of 1 mg/kg/day were often required for flares. Methotrexate was added in November 1996. However, despite doses up to 20 mg per week, she remained symptomatic.

**Table 1. Criteria for the diagnosis of adult onset Still’s disease (Yamaguchi et al. 1992 [28]). Five or more criteria (including two major) required for diagnosis**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Fever &gt; 39°C</td>
<td>Sore throat</td>
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<tr>
<td>Arthralgias</td>
<td>Lymphadenopathy or splenomegaly</td>
</tr>
<tr>
<td>Still’s rash</td>
<td>Hepatic dysfunction</td>
</tr>
<tr>
<td>Neutrophilic leucocytosis</td>
<td>Negative RF and ANA</td>
</tr>
</tbody>
</table>

ANA, antinuclear antibody; RF, rheumatoid factor.

**Table 2. Positive/abnormal tests**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate (mm.h)</td>
<td>120</td>
<td>(0–20)</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>21.6</td>
<td>0–0.8</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>7.9</td>
<td>12–15</td>
</tr>
<tr>
<td>White blood cell count (&lt;10 mm³)</td>
<td>25.6</td>
<td>3.4–10</td>
</tr>
<tr>
<td>Aspartate transaminase (U/L)</td>
<td>88</td>
<td>11–32</td>
</tr>
<tr>
<td>Alanine transaminase (U/L)</td>
<td>65</td>
<td>5–30</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>317</td>
<td>110–205</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>9846</td>
<td>12–250</td>
</tr>
</tbody>
</table>

**Table 3. Negative/normal tests**

- Antinuclear antibodies
- Anti-double-stranded DNA antibodies
- Anti-Smith
- Anti-Ro
- Anti-La
- Anti-RNP
- C3
- C4
- Rheumatoid factor
- ANCA
- Serum protein electrophoresis
- Creatine kinase
- Angiotensin converting enzyme concentration
- Anti-cardiolipin antibody
- Familial Mediterranean fever genetic test
- Lyme antibody
- VDRL test
- Purified protein derivative
- Cytomegalovirus (buffy coat, urine)
- Human immunodeficiency virus antibody
- Cultures: blood, urine, cerebrospinal fluid, bone marrow, broncho-alveolar lavage fluid

**Table 4. Pathology reports**

<table>
<thead>
<tr>
<th>Biopsy site</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>Marked granulocytic hyperplasia; no dysplasia</td>
</tr>
<tr>
<td>Liver</td>
<td>Patchy periportal inflammation; moderate steatosis</td>
</tr>
<tr>
<td>Cervical lymph node</td>
<td>Non-specific reactive histology</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>Normal histology with no lymphoid infiltrate or evidence of epithelial malignancy</td>
</tr>
<tr>
<td>Spleen</td>
<td>Follicular hyperplasia; negative for lymphoma</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Mild villous atrophy; Congo Red stain negative for amyloid</td>
</tr>
</tbody>
</table>
Methotrexate was stopped in October 1997 because of treatment failure. Over a 2-yr period, she needed more than 20 admissions to the medical ward for flares of AOSD. These were manifested as high fevers, evanescent rash, arthralgias, abdominal pain, an impressive leucocytosis (average 20 000–30 000 cells/mm³) and high serum ferritin levels. A typical admission lasted 2–3 days and consisted of multiple investigations, primarily aimed at ruling out an infectious aetiology in a splenectomized patient. After another flare in May 1998, however, she experienced an 8-month period during which her disease was quiescent. In January 1999, her disease flared again, requiring admission almost monthly for management of flares.

In May 1999, she was admitted with generalized weakness, postural dizziness, painful oral ulcers, facial paraesthesias and an acute onset of watery diarrhoea. Initial examination confirmed severe orthostatic hypotension (standing blood pressure 50/25 mmHg). She was afebrile and there was no rash. Ragged-edged and shallow based ulcers were noted on the tongue, buccal mucosa and gingiva. Neurological examination was remarkable for diffuse and symmetric weakness (graded 4–5 throughout) and absence of both deep tendon and corneal reflexes. During the next 2 days, she developed diplopia (without objective extraocular muscle dysmotility), dysphagia and facial diplegia. Magnetic resonance imaging of the brain showed no significant abnormality. Examination of cerebrospinal fluid revealed markedly elevated protein (421 mg/dl) but a normal opening pressure, cell count and glucose. Gram stain and bacterial and fungal cultures were negative. Biopsy of the oral lesions was consistent with aphthous ulcer and the Tzanck smear for herpes infection was negative. Nerve conduction studies demonstrated a substantial lag time in combined potentials, suggestive of a demyelinating process (Fig. 2).

These findings were consistent with the Miller Fisher variant of GBS. She was treated with pooled intravenous immunoglobulin 2 mg/kg/day for 3 days. Her cranial nerve palsies resolved within 1 week and she was discharged to a nursing home for rehabilitation.

After discharge, the areflexia has persisted and her strength has improved only marginally. Her course has been complicated by malnutrition and weight loss, necessitating gastrostomy tube feeding. She is ambulatory, but has been unable to work or independently care for herself and her two children.

Discussion

Still’s disease, first described by George Still in 1896, is the systemic form of juvenile rheumatoid arthritis [6]. Bywaters in 1971 described fourteen adults with an illness resembling Still’s disease and coined the term AOSD [7].

![Fig. 1. X-ray demonstrating non-erosive fusion of carpal bones in a pericapitate pattern, a distinctive feature of AOSD.](image1)

![Fig. 2. F response abnormality: right tibial F response, 13 traces. Minimal F response is prolonged at 61.8 ms (normal < 50 ms).](image2)
### Table 5. Neurological involvement of AOSD: review of the English literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cases</th>
<th>Sex/age</th>
<th>AOSD characteristics</th>
<th>Neurological findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reginato et al. 1987 [2]</td>
<td>3 (of authors' own patients)</td>
<td>20/F</td>
<td>Fevers, arthritis, sore throat, rash</td>
<td>(1) Acute disorientation, hallucinations during high fever (preceding liver failure) (2) Asterixis, mental status confusion, increased intracranial pressure during liver failure (3) Lower motor neurone facial nerve palsy during acute flare</td>
<td>First two patients had improvement in neurological symptoms with resolution of liver failure while on high-dose steroids Third patient had residual Bell's palsy after steroid therapy Overall, only one patient had a true manifestation of a neurological disorder with an acute flare of Still’s disease. The other two were complicated by liver failure</td>
</tr>
<tr>
<td>Garrote et al. 1993 [14]</td>
<td>16/M</td>
<td>Sore throat, myalgia, arthralgia, headache and vomiting, rash, fever and hepatosplenomegaly present on admission</td>
<td>Transient diplopia, oscillopsia, horizontal nystagmus on left gaze, paraesthesiae, dysaesthesias on left side of face, unstable gait, weakness upper right extremity and dorsus right ankle CT with hypodensity in left pons; MRI with T2 hyperintensity on left middle cerebellar and cerebral peduncles</td>
<td>Neurological symptoms resolved prior to non-steroidal therapy. The authors hypothesize that the neurological manifestations may be due to vascular involvement of the CNS and may be focal and transient; however, it is not clear that it is associated with AOSD as it resolved without therapy</td>
<td></td>
</tr>
<tr>
<td>Denault et al. 1990 [15]</td>
<td>20/M</td>
<td>Headache, fever, cough, myalgias and weight loss with development of arthritis later in the course</td>
<td>Neck stiffness, confusion, decreased consciousness and incontinence. CSF pleocytosis noted. CT normal. Mentation slowly improved without therapy. Two months later patient developed sensorimotor peripheral neuropathy documented by NCV and sural nerve biopsy</td>
<td>Evidence of meningoencephalitis: resolved without therapy raising the issue of whether it was related to Still’s disease or a presentation of an initial viral illness The sensorimotor peripheral neuropathy resolved with steroid therapy</td>
<td></td>
</tr>
<tr>
<td>Ohta et al. 1990[4]</td>
<td>Age/Sex not specified</td>
<td>Unknown in specific cases. All patients had definite Still’s fever, joint symptoms, rash, lymphadenopathy</td>
<td>5 with peripheral neuropathy; 4 with aseptic meningoencephalitis; 1 with delirium, confusion, rigidity (1 person had both peripheral and CNS involvement)</td>
<td>No discussion in paper of timing of diagnosis, i.e. acute flare of Still’s or not, association with other complications, etc.</td>
<td></td>
</tr>
<tr>
<td>Pouchot et al. 1991 [1]</td>
<td>Age/Sex not specified</td>
<td>Unknown in specific cases; Patients had diagnosis of AOSD based on Medsger and Christy criteria</td>
<td>2 patients with disorientation and confusion who developed hepatic failure; 1 patient with peripheral facial nerve palsy; 2 patients with transient deafness (not due to ASA); 1 patient with vertical diplopia with ptosis due to 3rd nerve palsy</td>
<td>No details of timing of diagnosis, resolution of symptoms or timing with therapy; however, patients with disorientation and confusion also had AOSD related hepatic failure</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>No. of cases</td>
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| Ohta et al. 1987 [3]            | Review of 228 cases of AOSD from the literature; 11 patients with neurological symptoms | Unknown in specific cases | 3 patients with meningoencephalopathy  
1 patient with brainstem haemorrhage  
1 patient with status epilepticus  
1 patient with pyramidal syndrome  
2 patients with CNS abnormalities  
2 patients with cranial nerve paresis  
1 patient with orbital pseudotumour | French; Ohta's own 2 patients  
See [16]  
See [27]  
French paper  
See Baker et al. [17]  
French paper; see [18]  
See [25] |
| Wouters et al. 1985 [16]        | 1            | 33/M    | High fever, evanescent rash, polyarthritis               | Patient developed diplopia and ptosis of left eyelid after having a total hip replacement; CT with small haemorrhage in brainstem. Patient presumably with active flare given significant polyarthritis | Paper not specific on activity of disease but presumably active with polyarthritis. Prednisone therapy relieved polyarthritis. No mention of neurological complications/resolution |
| Baker et al. 1979 [17]          | 2            | Age/sex not specified | Spiking fever, evanescent rash, polyarthritis, leucocytosis | Abstract mentions CNS manifestations in two patients. Unclear if two patients with acute liver failure who developed delirium and encephalopathy with increased ICP were those two patients | If 2 patients described with liver failure and mentation difficulties are the 2 with CNS manifestations, this would not qualify as a direct result of AOSD |
| Kaplinsky et al. 1980 [18]      | 1            | 34/F    | Polyarthralgia, fever, rash                              | Facial nerve paresis ‘that has been present since childhood’                          | No relationship between AOSD and neurological complications |
| Marie et al. 1999 [12]          | 1            | 17/M    | Headache, left 7th cranial nerve palsy, sore throat, high fever, arthralgias, myalgia, lymphadenopathy and meningeal syndrome | 7th cranial nerve palsy  
Meningeal symptoms with CSF showing lymphocytosis  
CT scan normal | Treatment with high dose aspirin resulted in complete resolution of symptoms. There appears to be a true relationship between the AOSD and a neurological condition |
| Markusse et al. 1988 [20]       | 1            | 26/M    | 9 year history of fevers, evanescent rash, arthralgias, lymphadenopathy, leucocytosis and liver enzyme abnormalities | Gradual development of hearing loss and tinnitus on admission with fevers, arthritis, rash, and weight loss. CT normal, CSF low cell count; indomethacin treatment stopped—hearing loss remained. Improved with prednisone; all other symptoms improved | All studies pointed to cochlear involvement, not related to indomethacin, all occurring during acute AOSD flare. This case supports an association between neurological conditions and AOSD |
| Scully et al. 1989 [21]         | 1            | 59/F    | Patient initially had a facial palsy with resolution. 1 week later patient developed sore throat, weakness and fevers | Facial palsy preceded symptoms of AOSD and resolved within 1 week | Unclear if AOSD and neurological symptom were related. NEJM discussant describes three other patients with lymphocytic meningoencephalitis, transient bilateral third cranial nerve palsy, and unilateral peripheral facial nerve palsy of 3 months duration. Timing of diagnosis, resolution of symptoms, etc. is not further described |
| Cush et al. 1985 [22]           | 1            | 21/M    | Fever, chills, sweats, sore throat, myalgia and anorexia, leucocytosis | Patient developed ptosis of the right eye with diplopia and orbital pain on lateral gaze. CT normal. Patient developed ptosis in the left eye along with fever and confluent rash | All symptoms resolved with anti-inflammatory therapy. Patient was believed to have developed an acute inflammatory orbital pseudo-tumour |
Nervous system involvement has been described in approximately 7–12% of patients with AOSD [1, 4]; however, neither the GBS nor the Miller Fisher syndrome (MFS) has been described before in a patient with AOSD. We present the first case report of a patient with AOSD who developed the Miller Fisher variant of GBS. Our patient had the characteristic findings of MFS confirmed by electromyographic studies.

GBS is characterized by progressive symmetrical limb weakness, areflexia, absent or mild sensory signs and variable autonomic dysfunctions. C. Miller Fisher described a syndrome consisting of ophthalmoplegia, ataxia and areflexia [8]. He regarded this syndrome as a variant of GBS; however, the relationship between MFS and GBS is controversial. Many patients with GBS and MFS report an antecedent, acute infectious illness or gastroenteritis that often resolves at the onset of neurological symptoms, such as our patient demonstrated. *Campylobacter jejuni* has been recognized as the most frequent antecedent pathogen for GBS and has also been reported in the Miller Fisher variant syndrome [9, 10]. Immune responses against *C. jejuni* have been postulated to be involved in both GBS and MFS by induction of a specific anti-ganglioside antibody which cross-reacts with neural tissues [11]. In GBS the specificity of anti-ganglioside antibodies is very variable and the presence of anti-GM1 ganglioside IgG antibodies may be associated with a more severe form of GBS. High titres of anti-GQ1b antibodies were found in MFS patients, as opposed to control subjects [12, 13]. Although we did not detect the anti-ganglioside antibody we believe that our patient’s antecedent diarrhoeal illness was probably related to the subsequent development of the MFS. It is not possible to speculate whether this patient’s MFS was causally related to her AOSD as the immunological basis of AOSD still remains unclear. It is interesting to postulate that the two disorders may share an infectious trigger, thus allowing the presentation of one with another.

A review of literature on neurological manifestations of AOSD revealed multiple problems with the case reports (Table 5). It is notable that in many case reports the neurological manifestations have no relationship to AOSD. Neurological syndromes, such as encephalopathy, delerium and decreased mentation, are often described in the literature as neurological complications of AOSD when they could be the manifestations of acute liver failure secondary to AOSD. Some neurological manifestations are reported during the acute phase of AOSD but resolve prior to appropriate therapy with anti-inflammatory medication, making it less likely to be related to the original disease. In most references it is difficult to distinguish a neurological complication associated with AOSD from a separate complication entirely. Overall, the review of the literature shows that there is a trend for some neurological complications, such as cranial nerve paresis, peripheral neuropathy and meningoencephalitis, to be associated with AOSD or a flare.
The diagnosis of AOSD is often difficult as it mimics systemic infections, systemic vasculitis or even neoplastic conditions such as lymphoma. As our case demonstrates, neurological manifestations can complicate the picture further.

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References