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A Case of Miller Fisher Syndrome, Thromboembolic Disease, and Angioedema: Association or Coincidence?

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Male, 32
Final Diagnosis: Miller Fisher syndrome
Symptoms: Ataxia • headache • ophthalmoplegia
Medication: —
Clinical Procedure: Plasmapheresis
Specialty: Neurology

Objective: Rare co-existance of disease or pathology

Background: Miller Fisher Syndrome is characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia, and is considered to be a variant of Guillain-Barre Syndrome. Miller Fisher Syndrome is observed in approximately 1–5% of all Guillain-Barre cases in Western countries. Patients with Miller Fisher Syndrome usually have good recovery without residual deficits. Venous thromboembolism is a common complication of Guillain-Barre Syndrome and has also been reported in Miller Fisher Syndrome, but it has generally been reported in the presence of at least one prothrombotic risk factor such as immobility. A direct correlation between venous thromboembolism and Miller Fisher Syndrome or Guillain-Barre Syndrome has not been previously described.

Case Report: We report the case of a 32-year-old Hispanic male who presented with acute, severe thromboembolic disease and concurrently demonstrated characteristic clinical features of Miller Fisher Syndrome including ophthalmoplegia, ataxia, and areflexia. Past medical and family history were negative for thromboembolic disease, and subsequent hypercoagulability workup was unremarkable. During the course of hospitalization, the patient also developed angioedema.

Conclusions: We describe a possible association between Miller Fisher Syndrome, thromboembolic disease, and angioedema.

MeSH Keywords: Angioedema • Guillain-Barre Syndrome • Miller Fisher Syndrome • Thromboembolism

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/901940

Background

The triad of ataxia, areflexia, and ophthalmoplegia was first described as a variant of Guillain-Barre syndrome in 1932 by James Collier [1]. In 1956, Charles Miller Fisher reported three patients who demonstrated the triad of ataxia, areflexia, and ophthalmoplegia without having prominent signs of peripheral neuropathy [1]. Miller Fisher Syndrome (MFS) is a geographically variable variant of Guillain-Barre Syndrome (GBS) observed in approximately 1–5% of all GBS cases in Western countries, yet in up to 19% and 25% in Taiwan and Japan, respectively [2]. There is an established male predominance at a ratio of 2: 1 [1]. Mean age of onset is 43.6 years, although cases of MFS have been reported in all age ranges [1,3]. As in GBS, an antecedent infectious illness can be identified in the majority of MFS cases [4]. Upper respiratory tract infection is the most commonly described prodromal entity, followed by gastrointestinal illness [1,4,5]. Molecular mimicry between GQ1b (a ganglioside component of the nerve) and the lipooligosaccharides of *Campylobacter jejuni* and *Haemophilus influenza* has been previously reported [6]. MFS is largely a clinical diagnosis, while serological confirmation with anti-GQ1b antibody allows for greater diagnostic certainty in the face of confounding symptoms [4]. Patients with MFS usually have good recovery and no residual deficits [2].

There is very little published information about thromboembolic complications of MFS; however, in GBS, deep vein thrombosis (DVT) is considered to be common [7]. Immobility, mechanical ventilation, and intravenous immunoglobulin (IVIg) therapy are common risk factors in GBS patients predisposing them to thromboembolic diseases [7,8]. However, the concomitant presence of both thromboembolic disease and GBS or MFS in a patient, without having an acquired or hereditary risk factor for thrombophilia, has not been previously documented in the literature. Moreover, no association has been previously reported between angioedema and GBS or MFS. We report an unusual case of MFS in which the patient had concurrent severe acute thromboembolic disease and developed angioedema during the acute phase of his illness.

Case Report

A 32-year-old Hispanic male with a history of alcohol abuse was referred to our hospital for the management of renal vein thrombosis and inferior vena cava (IVC) thrombosis. Three days prior to his transfer, the patient had presented to an outside hospital with nausea, vomiting, headache, decreased vision, and diplopia for two weeks. He was admitted for acute kidney injury (Cr: 2.32 mg/dL) and was found to have severe iron deficiency anemia (Hb: 7 g/dL), renal vein thrombosis, IVC thrombosis, and pulmonary emboli (PE). Two units of packed red blood cells were transfused. The hemoglobin level increased to 8.9 mg/dL and subsequently remained stable. Anticoagulant therapy was not started due to a reported episode of melena that had resolved prior to admission. The patient otherwise denied any hematemesis, diarrhea, fever, cough, seizures, or immobility. Supportive treatment resolved the patient's acute kidney injury.

Mechanical thrombectomy of the IVC was successful, while thrombectomy of the left renal vein was attempted but ultimately unsuccessful. Superior extension of the thrombus to the suprarenal IVC prevented the placement of an IVC filter. Anticoagulant therapy with unfractionated heparin was initiated upon admission to our hospital. On admission, the patient complained of retro-orbital and occipital headache and pain in the upper back and neck that was persistent, 6/10 in severity, and exacerbated with lying down. He denied nausea, vomiting, or photophobia. The patient also complained of bilaterally decreased vision, double vision, and fatigue. No fluctuation or diurnal variation of the symptoms was noticed. Past medical history and family history were negative for thromboembolic, neurologic, or rheumatologic diseases. He denied any history of prescribed medicines or herbal supplements. The patient did report binge drinking 6–12 beers per day with liquor during the previous 6 months in addition to occasional drinking for the past 10 years. His last drink was two weeks prior to his presentation to the outside hospital. He reported occasional methamphetamine use and was a former smoker.

Vital signs, weight, and body mass index upon admission were within normal limits. The patient was alert and oriented to time, place, person, and event. Speech was normal. Ocular exam revealed visual acuity of 20/20 and 20/30 in the right and left eyes respectively, severe bilateral restriction of eye movements in all directions, mild bilateral ptosis, symmetrically reactive pupils, absence of nystagmus, and normal ophthalmoscopic exam. Facial motor expression was bilaterally decreased. Other than the 3rd, 4th, 6th, and 7th nerves, the cranial nerves were intact.

On sensory exam, light touch was decreased in all extremities. Pinprick, temperature, and proprioception were intact and symmetric. Vibration sensation was impaired in the left lower extremity. Motor strength was 4/5 in both upper extremities, and 5/5 in both lower extremities. Deep tendon reflexes were trace in the brachioradialis, biceps, and triceps. Patellar and Achilles reflexes were bilaterally absent. Plantar reflex was downward. Gait was ataxic, and the patient was unable to stand without support. Tests of finger to nose, heel to shin, and rapid alternating movements were ataxic with the right side being worse. There were no other abnormal findings on the physical exam.

Based on the complete external ophthalmoplegia, ataxia, and areflexia, the patient was diagnosed with the Miller Fisher

variant of Guillain-Barre Syndrome. Anti-GQ1b antibody testing was ordered with the initial consideration of MFS; however, the sample was collected after plasmapheresis was initiated, possibly decreasing the sensitivity of the assay. Brain magnetic resonance imaging and magnetic resonance venography were unremarkable, with no evidence of acute stroke, hemorrhage, mass, cavernous sinus thrombosis, or white matter/cortical lesions. Lumbar puncture was not performed due to the risks of withholding anticoagulant therapy. Plasmapheresis was initiated three days after admission and was continued every other day for five sessions. Intravenous immunoglobulin therapy was considered but not administered because of concurrent venous thrombosis. Liver function tests during the first few hospital days showed mild to moderate rise in transaminases (Table 1) that resolved within five days. Viral hepatitis panel and human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay (ELISA) were negative. Hypercoagulability workup including lupus anticoagulant, antinuclear antibodies (ANA), anticardiolipin antibodies, factor V Leiden, prothrombin gene mutation assay, protein C activity, protein S activity, and beta-2 glycoprotein were all normal (Table 1). Antithrombin III activity was just below the normal range at 79% (reference range: 80–120%).

Our patient developed sinus tachycardia (heart rate up to 131/min) that required administration of metoprolol (12.5 mg twice a day). On day 9 after admission, he developed severe upper and lower lip swelling that was not associated with urticaria, pruritus, or respiratory symptoms. There was no history of allergy or similar symptoms in the past. Bradykinin-dependent angioedema was suspected. The patient had no history of angiotensin converting enzyme inhibitor use, and complement component C4 was normal.

The patient was transitioned to warfarin therapy and discharged after his last session of plasmapheresis. The general fatigue and gait improved slightly during the hospital stay; however, the external ophthalmoplegia remained unchanged until discharge. The anti-GQ1b antibody test was negative. At the follow-up visit 4 weeks after discharge, the ophthalmoplegia had nearly resolved. Weakness, ataxia, and headache were improving, and no new or recurrent thromboembolic events had occurred.

Discussion

Our patient demonstrated all three components of the characteristic triad (external ophthalmoplegia, ataxia, and areflexia) of MFS [1,9]. In addition to the triad, he had blepharoptosis, facial motor weakness, decreased visual acuity, mild upper extremity weakness, headache, and upper back pain, which are all consistent with the diagnosis of MFS and have been previously reported [1,10,11]. Sinus tachycardia could be a manifestation of autonomic dysfunction, which has also been reported in MFS [12].

MFS is largely a clinical diagnosis, as described by Miller Fisher in 1956 [13]. In 1992, Chiba et al. reported the presence of anti-GQ1b antibodies in strong association with MFS [14]. According to a study of 466 MFS patients reported by Ito et al. in 2008, anti-GQ1b antibody were present in 83% of MFS patients while 7% of MFS patients were negative for GQ1b but positive for at least one of the other anti-ganglioside antibodies (GT1a, GM1b, GalNAc-GD1a, and GD1b) [15]. A recent study showed that detection of serum IgG antibodies against GQ1b-related antigens was calcium dependent [16]. These authors demonstrated that when Tris-buffered saline (TBS; 20 mM Tris-HCl, PH 7.4, 150 mM NaCl) was used instead of phosphate-buffered saline during the ELISA test, IgG antibodies against GQ1b-related antigens were detected in 73% of the patients who were seronegative in the conventional assays [16].

The absence of anti-GQ1b antibodies in our patient could be related to the calcium dependency of the antibodies, the involvement of anti-ganglioside antibodies other than those against GQ1b, the initiation of plasmapheresis prior to initial antibody testing, or the patient possibly being among the small proportion of the MFS patients who are seronegative. However, based on the typical clinical presentation, remarkable improvement, and disease course, we believe that the diagnosis of MFS was clinically accurate.

The patient's transient transaminitis was likely driven by his alcohol abuse, although drug side effects (anesthetics, acetaminophen) and/or the possible preceding infection could have also been contributing factors. As of note, transaminitis has been reported in some cases of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *Campylobacter jejuni* infections [17–19].

The patient had concurrent venous thromboembolism (VTE) and PE, and developed angioedema. In previous studies, VTE/PE has been mentioned as a common complication of GBS [7] and has also been reported in MFS [1]. However, in those studies, increased risk of thromboembolism was generally attributed to immobility [7], mechanical ventilation [7], or IVIg therapy [8]; and VTE/PE events occurred only when at least one risk factor for thromboembolism was present [7].

Thromboembolic disease

We observed an MFS patient who was found to have severe acute thromboembolic disease upon presentation, prior even to the formal diagnosis of MFS. He was fully ambulatory at that time and did not have any history of recent trauma, recent hospitalization, or a previous thrombotic episode. A full

Table 1. Laboratory data findings.

Variable	Reference Range	Day 1#	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 38
Lupus dRVVT screen (S)	≤45											31			
Lupus PTT LA screen (S)	≤40											34			
Antinuclear antibody (ANA)	Neg.				Neg.										
Cardiolipin Ab IgA	APL*		<11												
Cardiolipin Ab IgG	GPL**		<14												
Cardiolipin Ab IgM	MPL***														
Factor V Leiden									Not found						
Prothrombin gene assay												Normal			
Protein C activity	70–180%		71												
Protein S activity	70–150%		72												
Antithrombin III activity	80–120%		79												
β2 glycoprotein I Ab (IgA)	≤20 SAU##								< 9						
β2 glycoprotein I Ab (IgG)	≤20 SGU##								< 9						
β2 glycoprotein I Ab (Ig M)	≤20 SMU##								< 9						
Total bilirubin (mg/dL)	0.2–1.0	0.7	0.9	1.5	0.7	0.6	0.4	0.6	0.5						
LDH (IU/L)	87–241												148		
Haptoglobin (mg/dL)	43–212												119		
Serum albumin (g/dL)	3.4–5.0	3.1	2.5	2.8	2.8	3.8	3.6	4.1	3.8			4.3			
AST (IU/L)	15–37	131	453	237	97	38	34	21	14						
ALT (IU/L)	12–78	151	158	149	129	60	63	31	30						
BUN (mg/dL)	7–18	12	14	10	9	5	6	5	8	6	11	8	6	5	
Serum creatinine (mg/dL)	0.7–1.3	0.97	1.00	0.94	0.92	0.86	0.96	1.05	0.92	0.94	0.97	0.91	0.84	0.86	
Anti-GQ1b Ab	Titer								<1/100						<1/100

Table 1 continued. Laboratory data findings.

Variable	Reference Range	Day 1[#]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 38
C4 Complement (mg/dL)	16-47										23				
ACh. receptor binding Ab	nmol/L[&]				<0.30										<0.30
Thiamine (nmol/L)	78–185				2200										

[#] Day 1 is the first day of admission at our hospital. * Reference ranges for cardiolipin IgA: ≤11: negative; 12–20: intermediate; 21–80: low to medium positive; >80: high positive. ** Reference ranges for cardiolipin IgG: ≤14: negative; 15–20: intermediate; 21–80: low to medium positive; >80: high positive. *** Reference ranges for cardiolipin IgM: ≤12: negative; 13–20: intermediate; 21–80: low to medium positive; >80: high positive. [##] SAU – standard A unit; SGU – standard G unit; SMU – standard M unit. [&] Reference ranges for acetylcholine receptor binding antibody: negative: ≤0.30 nmol/L; equivocal: 0.31-0.49 nmol/L; positive: ≥0.50 nmol/L.
dRVVT – dilute Russell viper venom test; S – second; PTT LA – partial thromboplastin time lupus anticoagulant; LDH – lactate dehydrogenase; AST – aspartate aminotransferase; ALT – alanine aminotransferase; BUN – blood urea nitrogen; ACh – acetylcholine.

hypercoagulability workup was performed, and all the studies were normal. One possible risk factor present in our patient was his alcohol use disorder as shown by Zöller et al. [20], although other studies have demonstrated contradictory associations [21], some of which indicate a significant protective effect of moderate alcohol consumption on development of VTE [22–25]. Thromboembolic disease in this patient would not be attributed to the coagulation imbalance seen in cirrhotic patients, as the clinical, laboratory, and imaging findings were not consistent with cirrhosis or hepatic failure. The presence of prerenal azotemia on admission in our patient likely indicates a period of severe dehydration, which could be a contributing risk factor, although the temporal relationship of dehydration and thrombosis is unknown. Overall, however, the severe thromboembolic disease in this patient appears out of proportion to his possible risk factors, and we hypothesize that there might be an association between the inflammatory process of MFS and increased risk of thromboembolism.

In the available literature, a direct correlation of increased risk of thrombosis with GBS or MFS has not been described. However, a large number of autoimmune disorders or immune-mediated diseases are reported to be linked to an increased risk of thrombosis [26]. Some of the central features of the hypercoagulability induced by inflammation are cytokine induction of tissue factor expression, endothelial dysfunction, inhibition of the protein C system, and inhibition of fibrinolysis (increased plasminogen activator inhibitor 1 levels) [27]. Disequilibrium between inducers and inhibitors of coagulation and fibrinolysis pathways, due to pro-inflammatory mediators, has been proposed to influence the hypercoagulability state in these conditions [28]. It has also been suggested that micro-particles (irregularly shaped small vesicles of heterogeneous size released from the plasma membrane in a tightly controlled process after different stimuli) could contribute to inflammation-induced hypercoagulability states [28].

In a study done on 73 GBS patients by Gaber et al. in 2002 [7], the risk of thromboembolic complications seemed to be higher in the first two to three months of onset of the disease [7]. After three months, even with prolonged immobility, the patients did not appear to be at increased risk of DVT [7]. This may suggest that the process of the autoimmune disease could contribute to the risk of DVT, rendering a higher risk while the disease is active.

Another possibility is that the preceding infection in the process of GBS or MFS may increase the risk of thrombosis. Common preceding pathogens in GBS include *Campylobacter jejuni*, CMV, EBV, varicella-zoster virus (VZV), and *Mycoplasma pneumoniae* [9]. There are some reports indicating that these infections can be associated with an increased risk of thromboembolism. Onuigbo et al. in 2002 [29] demonstrated a case of atrial thrombus, DVT, and pulmonary thromboembolism complicating hemorrhagic *Campylobacter jejuni* colitis [29]. Human CMV infection can induce vascular damage and platelet activation, and subsequently cause thrombosis [30]. Also, EBV-associated VTE has been reported [31]. There is a report of several cases of transient protein C and S deficiencies following varicella infection [32]. Also, *Mycoplasma pneumoniae* infection can induce a hypercoagulable state through transient antiphospholipid antibody syndrome [33–35]. Finally, DVT has also been reported in association with Dengue fever [36], which has already been reported to be associated with GBS and neuro-ophthalmic involvement [37].

Table 2. Characteristics of hereditary, non-allergic drug-induced, and acquired forms of angioedema.

Type of angioedema	Description	C1-INH antigenic level	C1-INH functional level	C4	C1q	Anti-C1-INH antibodies
HAE I/II	Symptoms present in childhood	Low in HAE type I Normal or elevated in HAE type II	Low	Low	Normal	No
HAE-N (HAE-nC1-INH)	Similar to types I/II, but: older age of onset: 20–30 years Trigger factors: estrogens	Normal	Normal	Normal	Normal	No
Non-allergic ACEI-AAE	ACEI use	Normal	Normal	Normal	Normal	No
C1-INH-AAE	Associated with lymphoproliferative disorder, autoimmune disorders, or infection Older age of onset: >40 years	Low/normal	Low	Low	Low (in most cases)	In some cases

Table adapted and summarized from Craig TJ1, Bernstein JA, Farkas H et al: Diagnosis and treatment of bradykinin-mediated angioedema: outcomes from an angioedema expert consensus meeting. Int Arch Allergy Immunol, 2014; 165, 119–27. Copyright 2014 by S. Karger AG, Basel. Adapted with permission.
C1–INH – C1 inhibitor; HAE I/II – hereditary angioedema type 1 and 2; HAE-N – hereditary angioedema with normal C1 inhibitor; ACEI-AAE – angiotensin converting enzyme inhibitor-induced acquired angioedema; C1-INH-AAE – C1 inhibitor-related acquired angioedema.

Bradykinin-mediated angioedema

The patient also developed bradykinin-mediated angioedema. In the 2013 angioedema expert consensus meeting in Budapest [38], bradykinin-mediated angioedema was classified into four different categories (Table 2).

Although C1 inhibitor (C1-INH) was not measured in our patient, the serum C4 level was normal. The patient had no history of ACE-inhibitor use. Among the four groups [38] of bradykinin-mediated angioedema (Table 2), normal C4 levels without ACE-inhibitor use only fit with the diagnosis of hereditary angioedema with normal C1-INH (HAE-N), although the patient had no exposure to estrogen. HAE-N is associated with a Factor XII mutation in 30% of the subjects [39]. Decreased levels of plasminogen activator inhibitor (PAI), especially PAI 2, is probably the key abnormality in HAE-N [39]. In the contact activation system, FXII is classically activated by negatively charged surfaces [40], but in HAE-N, instead of negatively charged surfaces, FXII is cleaved and activated by plasmin [41]. In our patient, who was in the regression phase of acute DVT, plasmin rise might have been a possible triggering factor for angioedema. Killewich et al. [42] measured tissue plasminogen activator (tPA) activity in serial intervals after the onset of DVT and showed that tPA activity (which could be an indicator of plasmin level) started to increase one week after the onset of DVT and remained significantly elevated for at least 11 weeks [42].

There is evidence of complement system activation in both demyelinating and axonal subtypes of GBS [9], while angioedema is also closely related to the complement system [38]. The complement system and coagulation system are derived from a common precursor [43]; both cascades contain series of serine-proteases with evidence of some shared activators and inhibitors, such as factor XIIa (activated form of factor XII which is a coagulation protein) and C1 esterase inhibitor [43]. Based on the facts that complement pathways are activated in GBS [9] and that there are close and complex interactions between coagulation, fibrinolysis, and classic complement pathways [43] (and subsequently angioedema), we hypothesize that a possible linked pathogenesis might be present behind the simultaneous occurrence of MFS, thromboembolic disease, and angioedema in our patient.

MFS is a rare disease, and most of the current knowledge about MFS is based on case series, case reports, and review articles. Our patient with MFS and severe thromboembolic disease makes a significant contribution to the existing body of literature in this field. As thromboembolic disease can be frequently asymptomatic, its possible associations with other diseases, especially the rare diseases, could potentially remain obscure. This report helps inform the medical community of the possible associations we describe, and promotes further reporting of this phenomenon.

Further investigation is required to determine if there is an association between GBS/MFS and increased risk of thromboembolism through the mechanism of the disease itself and independent of subsequent prothrombotic conditions such as immobility. If such an association is proven, it may support prophylactic anticoagulation for GBS/MFS patients upon diagnosis, even without the presence of other venous thromboembolic risk factors.

Conclusions

There may be an association between GBS/MFS, VTE, and angioedema due to a linked pathogenesis. We suggest that MFS and GBS patients undergo screening for concurrent VTE upon initial diagnosis. This may lead to early detection and treatment of the thromboembolic diseases. Moreover, GBS and MFS patients may be exposed to prothrombotic treatments or conditions. If VTE is proven to be associated with the GBS/MFS, patient care may be conducted or modified accordingly; for example, IVIg therapy may promote thrombosis while plasmapheresis is equally effective and does not impose this side effect. Intensive physical therapy may improve the mobility and decrease the risk.

VTE can cause severe consequences. Exploring the possible association that we describe may lead to prevention and early detection of VTE, and deserves consideration.

Conflicts of interest

None.

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