Successful treatment of postural orthostatic tachycardia and mast cell activation syndromes using naltrexone, immunoglobulin and antibiotic treatment

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SUMMARY
A patient with severe postural orthostatic tachycardia syndrome (POTS) and mast cell activation syndrome (MCAS) received immunotherapy with low-dose naltrexone (LDN) and intravenous immunoglobulin (IVIg) and antibiotic therapy for small intestinal bacterial overgrowth (SIBO). A dramatic and sustained response was documented. The utility of IVIg in autoimmune neuromuscular diseases has been published, but clinical experience with POTS is relatively unknown and has not been reported in MCAS. As a short-acting mu-opioid antagonist, LDN paradoxically increases endorphins which then bind to regulatory T cells which regulate T-lymphocyte and B-lymphocyte production and this reduces cytokine and antibody production. IVIg is emerging as a promising therapy for POTS. Diagnosis and treatment of SIBO in POTS is a new concept and appears to play an important role.

BACKGROUND
These syndromes are generally regarded as rare or are never diagnosed owing to lack of awareness by physicians. The prevalence of postural orthostatic tachycardia syndrome (POTS) is at least 170/100 000, and the prevalence of mast cell activation syndrome (MCAS) is estimated between 1% and 1.7%. The confusing magnitude of symptoms led to delay in diagnosis and disability in our patient as is the case for the majority of patients with these syndromes. Fatigue, muscle pain, presyncope/syncope, headache, itching, urticaria, paraesthesia, nausea, chills, oedema, eye irritation, dyspnoea and heartburn are experienced by ≥50% of patients with MCAS. Postural lightheadedness especially in the morning, palpitations, presyncope, headache, blury vision, memory problems are experienced by ≥50% of patients with POTS. To further complicate matters, 17 of 48 MCAS symptoms overlap with 33 POTS symptoms which is explained by comorbidity of the syndromes, where 30% of patients with POTS also have MCAS. Gastrointestinal (GI) symptoms are common in both syndromes. GI symptoms in MCAS can be explained by inappropriate release of mediators from mast cells (MCs) with KIT mutations whereas GI motility disorders in POTS may be due to active autoimmune mucin carin antibodies causing autonomic imbalance in some patients (S Vernino, personal communication, 2017). Physicians may erroneously attribute these frequent GI symptoms in undiagnosed MCAS and POTS patients to irritable bowel syndrome (IBS) and psychological disturbances as was the case in our patient.

POTS is generally divided into two categories: neuropathic and hyperadrenergic; the latter is difficult to treat and is thought in part to be associated with MC as a driving force in some patients. POTS therapy has historically focused on treating orthostatic intolerance which does not address other systems (eg, GI tract, urinary bladder sphincter, ocular and central nervous system). MCAS therapy is directed at MC stabilisation, which is complicated by the fact that MC can release 200 mediators many of which have a wide array of triggers. Small intestinal bacterial overgrowth (SIBO) causes abdominal pain, bloating and abnormal bowel function—these symptoms are prevalent in both syndromes yet a specific investigation has not been reported. The dramatic response to therapy in this patient is remarkable and could help others who suffer from POTS and MCAS.

CASE PRESENTATION
Case
A 43-year-old Caucasian female F experienced MCAS symptoms at age 18: specific foods and odours caused flushing, rashes, itching, wheezing, diziness and nausea. At age 20, she noted problems with postprandial bloating/pain, constipation, evacuating stool and flatus with rotten egg odour. Restless legs syndrome (RLS) gradually developed. At age 23, she developed orthostatic lightheadedness and tachycardia, body pain, generalised weakness and painful dependent leg edema. Ultimately, she suffered from 45 individual clinically significant symptoms (table 1). For 6 years, she became disabled owing to orthostatic symptoms, fatigue and body pain. Faecal evacuation resulted in syncope with efforts >3 min. Early satiety led to a liquid diet. Pressure-induced hives and angioedema, paraesthesia and nocturnal urination (seven times nightly) interfered with sleep. Over 16 years, 19 physicians failed to diagnose POTS and MCAS which were established at a second location of the Mayo Clinic. Supine pulse of 80 beats/min increased to 160 after standing 10 min. Facial rash and oedema, cold, blue hands, Terry’s fingernails and dermatoglyphism were present (figure 1).
The patient is a biostatistician who did not smoke or drink. The family history was unremarkable.

INVESTIGATIONS

The tilt table test demonstrated the presence of hyperadrenergic POTS (increase in heart rate >30 beats/min, rise in systolic blood pressure ≥10 mmHg and serum norepinephrine level ≥600 pg/mL). The standing serum norepinephrine was 754 pg/mL (normal 119–451 pg/mL). Sudomotor testing revealed diminished postganglionic sympathetic function in feet. Abnormal tests included leukocytes 3.1 ×10^9/L, platelets 113 ×10^9/L, and total leukocytes 3.1 ×10^9/L. Abnormal tests also included lactate, cold agglutinins, and T3, and elevated 24-hour urine leukotriene E4 523 pg/mg creatinine (normal <104 pg/mg) and 11β-prostaglandin-F2α 1796 ng/mmol creatinine (normal <1000 ng/mmol creatinine). Normal tests included chemistry panels, lactate, cold agglutinins, tryptase, ferritin and 24-hour urine levels of metanephrine, N-methylhistamine and 5-hydroxyindoleacetic acid (5-HIAA). The patient had biochemical evidence for MC activity (two urine tests positive for α1-prostaglandin-F2α and one positive for β2-prostaglandin-F2α).

The family history was unremarkable.

Differential diagnosis in POTS includes: cardiac arrhythmia, venous insufficiency, chronic fatigue syndrome, anxiety and various GI disorders including acid reflux disease, gastric emptying disorders, pelvic floor dysfunction, IBS, carcinoid syndrome and pheochromocytoma. For this patient, all specific diseases and triggers known to cause POTS were excluded.

Continued
Novel treatment (new drug/intervention; established drug/procedure in new situation)

Figure 1 (A) Vasospasm with cyanosis and oedema, Terry’s nails, and facial flushing, rash and oedema; (B) After third intravenous immunoglobulin infusion, face returned to normal and hand colour, swelling and temperature improved. The patient gave her permission to use uncensored photographs.

data or serological evidence of traumatic brain and electrical injury, Lyme’s disease, human papillomavirus vaccination, pregnancy, median arcuate ligament syndrome, hypermobile Ehlers-Danlos syndrome (EDS) (present in 30% of POTS), coeliac disease, Sjogren’s syndrome, antiphospholipid syndrome, rheumatoid arthritis, lupus and common variable immunodeficiency. The norepinephrine was elevated but not to the level seen in carcinoid syndrome. Differential diagnosis of MCAS includes: chronic fatigue syndrome, fibromyalgia, generalised allergies, asthma, sinusitis, rosacea, anxiety, IBS, interstitial cystitis, carcinoid syndrome and pheochromocytoma. The duration of the illness and the 5-HIAA measurement excludes carcinoid syndrome.

TREATMENT

Thyroid replacement led to resolution of RLS. Hypothyroidism is a known cause for this syndrome. POTS vasoactive medications (midodrine, amphetamine and droxidopa), MCAS medications including cromolyn sodium, montelukast, antihistamines (hydroxyzine and all over-the-counter H1 and H2 blockers) and acetylsalicylic acid, support stockings, high salt diet and thyroid supplementation failed to give the patient any relief.

The patient studied low-dose naltrexone (LDN) and intravenous immunoglobulin (IVIg) on the Internet as alternative therapy for pain and POTS. As a scientist, the patient tracked symptoms which were later divided into three syndromes (table 1). In the absence of validated scoring systems for MCAS and POTS, the severity and frequency scores for symptoms were established by the authors as 10-point Likert scales: (A) Frequency: 0=never, 1=once a month or less, 2=1–3 times a month, 3=once a week, 4=a few times a week, 5=most days, 6=once a day, 7=a few times per day, 8=most of the time, 9=nearly constantly, 10=constantly, without exception and (B) Severity: 0=non existent, 1=very mild, 2=rather mild, 3=mild, 4=low moderate, 5=moderate, 6=high moderate, 7=starting to be severe, 8=severe, 9=extremely severe, 10=most severe possible. IBS studies have used Likert scores as well. More recently a combined response that includes a decrease in pain of 30% or more and improvement in stool form over a period of time have been used in drug studies; however, this was not felt to be as helpful in this single case report.

Her internist prescribed ultra-low-dose naltrexone (1 mg every night as opposed to dose escalation to ideal dose of 4.5 mg) while waiting for insurance approval for IVIg to be used for the Food and Drug Administration-approved indication of pressure-induced urticaria. Ultra-low-dose naltrexone for 6 weeks improved body pain, mood, memory, sleep, flushing, food and odour sensitivities and paraesthesia: 7% decrease in POTS and 17% decrease in MCAS severity scores. Subsequently, IVIg 1.5 g/kg (Privigen) and 125 mg methylprednisolone were administered monthly. Naltrexone was continued at 1 mg every night. Six days after the first IVIg infusion, syncope, tinnitus, anal outlet disorder and vascular spasm ceased. Capillary refill time was >1 min before IVIg and reduced to <2 s. The next two infusions further improved body pain, weakness, vertigo, ability to eat and facial changes. Subsequent infusions maintained symptomatic improvement but the efficacy did not improve further (figure 2). The platelet counts normalised when measured after the sixth infusion.

After GI consultation, the naltrexone dose was increased and a lactulose breath test (LBT), an indirect test for SIBO, was obtained.8 The LBT had a flat-line pattern suggesting excretion of hydrogen sulfide (H2S) which was confirmed by a prototype H2S breath test machine (Commonwealth Labs, Boston, Massachusetts, USA). Rifaximin 550 mg tablet per os three times a day for 2 weeks and a low sulfate/sulfid diet eliminated postprandial bloating, abdominal pain, constipation and foul gas. Subsequent dose escalations of LDN and short-term rifaximin improved therapeutic response curves: 24% decrease in POTS and 43% decrease in MCAS severity scores (figure 2).

OUTCOME AND FOLLOW-UP

After 10 IVIg treatments, a previously scheduled appointment at Mayo Clinic Scottsdale included autonomic testing which showed resolution of tachycardia with head-up tilt along with improvement in sudomotor function. At the time of submission of this report, the patient has had 20 IVIg treatments with a maximum of 5 weeks without one because the effects start to wear off. A trial of mycophenolate mofetil led to immune suppression. The next plan is to add new mast cell therapies in combination with IVIg and LDN.

DISCUSSION

A patient with severe POTS, MCAS and SIBO responded to a combination of LDN, IVIg and antibiotic therapy. We theorise...
Novel treatment (new drug/intervention; established drug/procedure in new situation)

that pre-existing MCAS was the driving force for hyperadrenergic POTS in this patient. This is the first case to our knowledge where immunotherapy with IVIg led to significant and sustained improvement in MCAS as has been seen in publications of autoimmune neuromuscular diseases and a single case of POTS.9 10 Other patients with MCAS have had response in their MC symptoms to IVIg.2 To our knowledge, this is also the first reported case of LDN improving symptoms of POTS and MCAS. Antibiotic therapy with rifaximin led to cessation of two decades of significant GI problems in our patient. Huang et al reported that 7/12 patients with POTS had dilated and/or air–fluid levels in the small intestine.11 We theorise that sustained sympathetic activity suppresses peristalsis, leading to stasis and development of SIBO in some patients with POTS. Alternative explanations for SIBO in POTS or MCAS who have concomitant EDS include presence of droopy small bowel loops or motor dysfunction due to protein deposition.12 We also theorise that eliminating SIBO can lessen MCAS and subsequent POTS by reducing intestinal permeability, thus reducing MC recruitment as well as T-cell activity and cytokines which activate MC.

In the present case, severe symptoms of MCAS preceded onset of POTS, thus, two driving forces are theorised to be important: mast cell activation adjacent to autonomic nerves and/or persistent recruitment and/or activation of MC due to bacterial overgrowth.4 7 13 It is less likely that an autoimmune neuropathic process is operative. However, we could not measure investigative adrenergic active autoantibodies and muscarinic acetylcholinesterase autoantibodies in order to include or exclude POTS-specific active autoantibodies (S Vernino, personal communication, 2017).14

One of the authors (BG) who reported successful treatment of POTS associated with Sjogren’s syndrome in 2017 has successfully treated over 50 subsequent patients.10 One of our GI clinic patients with POTS and MCAS treated with IVIg had improvement in cardiovascular symptoms and a dramatic cessation of the abdominal pain and diarrhoea which had triggered 250 emergency room visits over the past 15 years. Another GI clinic patient with POTS and SIBO but not MCAS was treated with IVIg had improvement in cardiovascular symptoms and later in GI symptoms after repeating antibiotic therapy. The change in this patient suggested that autoantibodies were operative.

One common mechanism for high-dose IVIg to work in autoimmune disease is binding the Fc portion of autoantibodies.9 MC are most commonly known to have IgE receptors, but they also have IgG receptors.15 When these are activated by IgG, histamine is released.15 Theoretically, IVIg could overload these receptors and ultimately reduce MC mediator release. IVIg could also bind to histamine and block histamine activation of MC as seen in rats.16 An additional trigger for MC activation includes T-cell activity and release of microparticles and cytokines.17 IVIg increases regulatory T-cells which could reduce T-cell activity and thereby reduce MC activity.18 Finally, IgG has been found to downregulate IgE bound to MC and thus binding IgG by IVIg could play an additional role.19

Figure 2 Change in mean syndrome symptom indexes with continuous administration of low-dose naltrexone (LDN) with dose escalation, monthly intravenous immunoglobulin (IVIg) starting 2 months later and a 2-week course of rifaximin. MCAS, mast cell activation syndrome; POTS, postural orthostatic tachycardia syndrome; SIBO, small intestinal bacterial overgrowth.
Beneficial effects of LDN on MCAS may include regulating overall T-lymphocyte production and decreasing cytokine mediators from T cells which directly cause MC activation, blocking Toll receptors which stimulate MC activity and reducing neuroinflammatory pain via microglia.12 20–22 Endorphins produced by LDN may improve intestinal dysmotility in POTS by directly increasing the migrating motor complex which prevents small intestinal stasis and subsequent bacterial overgrowth.23 We theorise that neuropathic POTS with an immune mechanism may also be improved by LDN via reduction of auto-immune antibody production by B-lymphocyte regulation.20

In a chart review of 33 additional patients with POTS in our GI clinic, 27 had lactulose breath testing (26 women, 1 men, mean age 33 years). These patients had MCAS in 27% and EDS in 42%. GI symptoms were present in all patients: mid/lower abdominal pain (96%), bloating (92%), nausea (85%), constipation (73%), diarrhoea (58%) and heartburn (58%). LBT was abnormal in 69% versus abnormal testing in 10% of volunteers in a prior control study.24 EDS did not increase the risk of having a positive breath test in our clinic patients. When methane was present, neomycin was added to rifaximin for 2 weeks since methane producing-bacteria respond best to dual antibiotics.25 Naltrexone was used by 11 patients and 7 had improvement in GI symptoms. Five had improvement in the other syndromes: two MCAS, one POTS and two with both. Antibiotics were administered to 15 patients: 10 had improvement in GI symptoms and 4 had improvement in POTS symptoms. One of these patients with POTS and MCAS improved dramatically to LDN therapy. Even though patients with POTS/MCAS improved dramatically to LDN therapy, antibiotics did not improve in LBT testing.

IVlg appeared to be effective for multiple manifestations of POTS but this treatment is expensive and has potential significant side effects. In contrast, LDN is inexpensive, safe and appeared to provide effective, adjunctive therapy in both MCAS and POTS. Recognition that small bowel dysfunction in POTS can lead to SIBO is important since antibiotic treatment can lead to significant GI relief.

Competing interests None declared.

Patient consent Obtained.

Learning points

► Patients with postural orthostatic tachycardia syndrome (POTS) and mast cell activation syndrome (MCAS) have a wide array of symptoms and require an open mind to entertain the diagnoses.

► POTS can imitate severe gastrointestinal motility disorders, irritable bowel syndrome (IBS), or frequent ‘IBS’ or small intestinal bacterial overgrowth (SIBO) relapses after antibiotic therapy.

► Treatments for hyperadrenergic POTS have had limited in efficacy but treatment directed at MCAS can help.

► Combined therapy with intravenous immunoglobulin and low-dose naltrexone led to significant improvement in a severely affected patient.

► Antibiotic therapy for SIBO contributed to clinical improvement in the case presentation and others in our practice for both GI symptoms and POTS/MCAS symptoms.
Novel treatment (new drug/intervention; established drug/procedure in new situation)

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