

## Editorial

### Atopic Conditions in Search of Pathogenesis and Therapy

Allergy and asthma have reached epidemic proportions, with almost 20% of Americans affected,<sup>1</sup> and both have been associated with obesity<sup>2</sup> and stress,<sup>3</sup> which are prominent in our society.<sup>4</sup> Moreover, there has been an emergence or recognition of a number of additional conditions that share many symptoms traditionally associated with classic allergic diseases. These conditions are quite distinct in that such patients are not typically allergic in the usual sense of having positive radioallergosorbent test and skin prick test results to known antigens.

Such conditions include mast cell activation syndrome (MCAS),<sup>5</sup> coronary hypersensitivity (Kounis) syndrome,<sup>6</sup> multiple chemical sensitivity (MCS) syndrome,<sup>7</sup> gluten intolerance without celiac disease,<sup>8</sup> food intolerance associated with attention-deficit/hypersensitivity disorder,<sup>9</sup> and autism.<sup>10</sup> Additional conditions include cyclic vomiting syndrome,<sup>11</sup> cystitis/bladder pain syndrome (IC/BPS),<sup>12</sup> myalgic encephalopathy or chronic fatigue syndrome (CFS),<sup>13</sup> and fibromyalgia syndrome (FMS).<sup>14</sup>

Most patients with MCAS present with abdominal pain or diarrhea, skin reactions and flushing, and headaches or memory and concentration difficulties (brain fog) associated with activation of the unique tissue immune cell, the mast cell (MC). MCAS should be suspected when there is unexplained multiorgan involvement in the absence of elevated serum tryptase levels.

In Kounis syndrome, patients experience sudden unexplained coronary events, often immediately after some hypersensitivity reaction, suspected to activate intracoronary MC to release proinflammatory mediators.

The MCS syndrome is a chronic condition characterized by not only nausea, fatigue, dizziness, and headaches but also inflammation of skin, joints, gastrointestinal tract, and airways, often resembling MCAS. These symptoms develop when patients are exposed to triggers that include smoke, pesticides, plastics, synthetic fabrics, scented products, and paints.

Autism is a neurodevelopmental disorder characterized by impaired social interactions, language loss, and repetitive behaviors. It is often precipitated after some infectious or stress trigger and can be associated with gastrointestinal and skin reactions.

Cyclic vomiting syndrome is a gastrointestinal disorder seen primarily in children, characterized by bouts of unexplained vomiting, often precipitated by stress that may overlap with MCS syndrome.

IC or BPS is defined as low pelvic pain or pressure associated with increased daytime frequency of urination and nocturia for more than 3 months in the absence of a urinary tract infection. Chronic prostatitis in men seems to be a similar condition, and the 2 together are now called urologic pelvic pain syndrome. They are often comorbid with CFS and FMS.

CFS is characterized by debilitating fatigue lasting longer than 6 months that is not relieved with rest, as well as at least 4 of the following: malaise after intense exercise, unrefreshing sleep, impaired memory or concentration (brain fog), muscle pain, polyarthralgia, tender lymph nodes, and new headaches. It is often comorbid with MCAS and FMS.

Patients with FMS present with long-term, body-wide pain and tenderness in the joints, muscles, tendons, and other soft tissues, typically reflected by sets of 9 painful tender or trigger points along the back. In addition, FMS is associated with fatigue, sleep disturbances, headaches, depression, and anxiety.

All these conditions involve sterile inflammation and worsen with stress, but the pathogenesis is unknown, thus hampering the development of effective treatments. A possible common link appears to be the MC<sup>15</sup> (Figure 1). For this reason, the Mastocytosis Society, with support from the American Academy of Allergy, Asthma, and Immunology, created a DVD to highlight MC involvement not only in allergy but also in many other conditions (Figure 2).<sup>16</sup> It is interesting that Hans Selye first wrote *The Stress of Life* in 1956<sup>17</sup> and then wrote a book entitled *The Mast Cell* in 1965<sup>18</sup> but never connected stress and MCs. It is now known that stress activates MCs through high-affinity surface receptors



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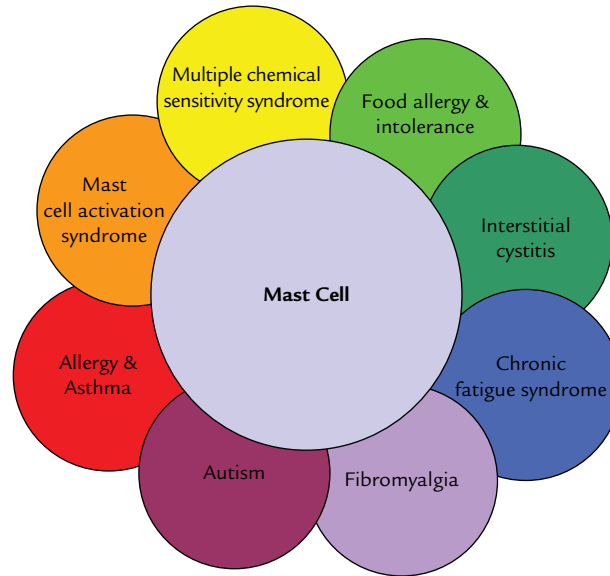


Figure 1. The suggested role of mast cells in the pathogenesis of a number of overlapping conditions that are often comorbid in the same patients.

for both corticotropin-releasing hormone and neurotensin that are released from dorsal root ganglia and have synergistic effects.<sup>19</sup> The effect of stress has been shown to be dependent on MCs in the brain,<sup>20</sup> lungs,<sup>3</sup> skin,<sup>21</sup> and bladder.<sup>22</sup> Moreover, MCs have the ability to release their numerous mediators selectively in a mode not discernable by routine histologic analysis,<sup>23</sup> indicating that MC stimuli and mediators involved in each of these conditions may be different.

Interestingly, it was recently reported that during MC degranulation, mitochondria undergo fission and move to the cell surface,<sup>24</sup> where they release mitochondrial DNA and other components that are misconstrued by the body as innate pathogens and induce a strong autoinflammatory response.<sup>25</sup> This finding could explain the inflammation present in many of the conditions discussed. It is also in line with the late Lynn Margulis' work that found that mitochondria are

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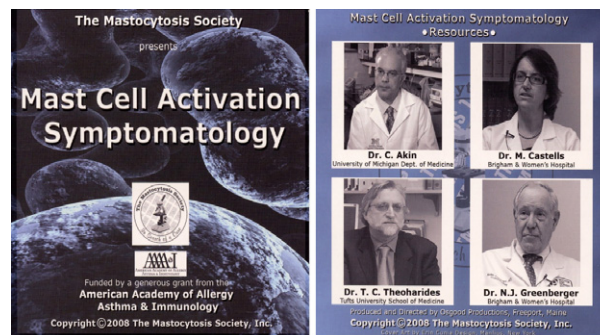


Figure 2. The front and back cover of the DVD produced by the Mastocytosis Society with support from the American Academy of Allergy, Asthma and Immunology to highlight mast cell involvement not only in allergy but also in many other conditions. Reprinted with permission from the Mastocytosis Society.

bacteria that become symbiotic with eukaryotic cells<sup>26</sup> or as the late Lewis Thomas stated in *The Lives of a Cell*, “. . . mitochondria . . . turn out to be little separate creatures, the colonial posterity of migrant prokaryocytes, probably primitive bacteria that swam into ancestral precursors of our eukaryotic cells and stayed there.”<sup>27</sup>

Given these findings, it would be reasonable to block MC activation. However, no drugs that can block MC secretion are clinically available. The so-called mast cell stabilizer disodium cromoglycate (cromolyn) is quite effective in rats<sup>28</sup> but has been recently shown *not* to inhibit human MCs.<sup>29-31</sup> Instead, the natural flavonoids luteolin and quercetin have potent anti-inflammatory and MC inhibitory actions.<sup>32,33</sup> In fact, dietary supplements containing these flavonoids have been reported to have significant benefit in IC and PBS<sup>34</sup> and autism.<sup>35</sup>

Recent epidemiologic data indicate that the conditions discussed together may affect as many as 1 in 100 people and have a major effect on health, society, and the economy. On average, patients with MCS syndrome spend >30% of their annual income on health-related costs.<sup>36</sup> The cost of autism has been estimated to be \$126 billion per year in the United States.<sup>37</sup> In the United States, CFS costs an estimated \$25 billion each year in medical costs and lost productivity,<sup>38</sup> whereas the cost for FMS is estimated at \$12 to \$14 billion per year.<sup>39</sup>

It is hoped that this editorial, along with the accompanying reviews and clinical studies, will raise awareness and stimulate necessary research for these conditions that are difficult to diagnose and even more difficult to treat.

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