LETTER TO THE EDITOR

Intestinal staphylococcal small colony variants: a cause of medically unexplained physical symptoms?

Irritable bowel syndrome (IBS) is often associated with food intolerances, fibromyalgia, and chronic fatigue (1), a symptom cluster commonly denoted as medically unexplained physical symptoms. We here present three cases which may give new thoughts concerning the etiology of the condition.

Case 1: A male veterinarian, age 57. At age 38, he was treated with several long-lasting courses of antibiotics due to epididymitis. He thereafter developed IBS and subsequently musculoskeletal pain and chronic fatigue. Following an open knee injury complicated with chronic infection with antibiotic-resistant *Staphylococcus epidermidis* at age 55, his systemic complaints deteriorated, forcing him to restrict his veterinary practice considerably. He himself had discovered similar bacterial growth from swabs of his own rectal mucosa as from the mucinous secretion of his injured knee.

Case 2: A male physician, age 60. At age 21, he got severe IBS following several courses of antibiotics due to recurrent airways infections. Subsequently, he gradually developed musculoskeletal pain and chronic fatigue which forced him to reduce his workload to less than the half. Some hearing loss and a slight aortic valve insufficiency were also diagnosed.

Case 3: A female physician, age 55. At age 35, she developed mild IBS following multiple courses of antibiotics for nasal sinusitis. Subsequently, she gradually developed mild mental fatigue and facial rosacea. At age 54, following an episode of acute gastroenteritis combined with stress related to the death of a near family member, she developed severe IBS. Simultaneously, she experienced worsening of her mental fatigue and the rosacea as well as having additional symptoms (such as joint stiffness). With considerable efforts, she maintains full job.

Common to all three cases is a normal routine physical and laboratory examination and no apparent cause of their abdominal and systemic complaints which also included food intolerances. Upper endoscopy was unremarkable. However, duodenal biopsies showed increased (but within normal limits) counts of intraepithelial lymphocytes (IELs), and the patients had all growth of numerous pin-point clear staphylococcal small colony variants (SCVs) in virtually pure culture, when brush samples from the duodenum were plated directly on mannitol salt agar. In a supplementary investigation, we examined 50 patients with similar symptomatology with brush samples from deep in the nasal cavity and from the rectal mucosa 3–4 cm above the anal sphincter. From these locations, all patients had growth of coagulase-negative staphylococci (CNS) in a mixed population with SCVs (Fig. 1).

CNS species are considered normal commensals on skin and mucosal membranes and therefore often ignored by clinicians. However, in both humans and animals, CNS is now a growing concern due to persistent infections at several body sites (2). By switching to a SCV phenotype, metabolism is slowed down, enabling intracellular growth and escape from antibiotics and immunological attacks (3). In fact, formation of SCVs may be a consequence of...
antibiotic therapy (4), as might be the case in the present cases. Extensive growth of CNS in the gastrointestinal tract of patients with IBS is therefore a potentially important finding. Some earlier studies with a staphylococcal vaccine suggested that staphylococcal infections may be involved in the pathogenesis of fibromyalgia and chronic fatigue (5), but we were unable to find reports on any relationship between staphylococcal infections and IBS. The present cases remind us that intestinal CNS, and maybe staphylococcal SCVs in particular, should not be neglected as a possible cause of IBS and associated conditions (1). The disease mechanisms may involve activation of innate immunity (note increased numbers of duodenal IELs), which in turn will modify tryptophan metabolism with a range of consequences including impaired brain and gut functions as outlined earlier (6).

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References

1. Berstad A, Undseth R, Lind R, Valeur J. Functional bowel symptoms, fibromyalgia and fatigue: a food-related triad? Scand J Gastroenterol 2012; 47: 914–9.
2. Proctor RA, von Eiff C, Kahl BC, Becker K, McNamara P, Herrmann M, et al. Small colony variants: a pathogenic form of bacteria that facilitates persistent and recurrent infections. Nat Rev Microbiol 2006; 4: 295–305.
3. Baddour LM, Simpson WA, Weems JJ, Jr, Hill MM, Christensen GD. Phenotypic selection of small-colony variant forms of Staphylococcus epidermidis in the rat model of endocarditis. J Infect Dis 1988; 157: 757–63.
4. Proctor RA, Kahl B, von Eiff C, Vaudaux PE, Lew DP, Peters G. Staphylococcal small colony variants have novel mechanisms for antibiotic resistance. Clin Infect Dis 1998; 27: 868–74.
5. Zachrisson O, Colque-Navarro P, Gottfries CG, Regland B, Mollby R. Immune modulation with a staphylococcal preparation in fibromyalgia/chronic fatigue syndrome: relation between antibody levels and clinical improvement. Eur J Clin Microbiol Infect Dis 2004; 23: 98–105.
6. Berstad A, Raa J, Valeur J. Tryptophan: ‘essential’ for the pathogenesis of irritable bowel syndrome? Scand J Gastroenterol 2014; 1–6. doi: 10.3109/00365521.2014.936034.