

Increased tissue permeability and sympathetic nervous system hypofunction may be the common link between dysmenorrhea, chronic pelvic pain, Mittelschmerz, and Crohn's disease

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Summary

Purpose: To determine if severe periovulatory diarrhea in a woman with Crohn's disease for just one day may be related to increased permeability of the large bowel related to hormonal changes that occur at this time of menstrual cycle. **Materials and Methods:** Dextroamphetamine sulfate was given to a woman whose Crohn's disease was markedly improved by adalimumab but who still had one day of severe diarrhea at mid-cycle. **Results:** She did not have any diarrhea or frequent defecation for the first two periovulatory times before she achieved pregnancy. Previously for two years there had not been one month where she did not have the severe periovulatory diarrhea. **Conclusions:** This case helps support the concept that the classic symptoms of Mittelschmerz in women with endometriosis may be related to periovulatory events which either cause increased permeability of an already compromised tissue, whether it be pelvic or bowel or other tissues, or these periovulatory events impair sympathetic nervous system function, which is already impaired.

Key words: Sympathetic neural hyperalgesia edema syndrome; Endometriosis; Mittelschmerz; Crohn's disease.

Introduction

It is common belief that women who get severe pelvic pain at certain specific times in the menstrual cycle, e.g., pre-menstrual or periovulatory, probably have endometriosis [1]. It is not clear how infiltrates of menstrual tissue can cause pain at the specific times.

Removal of the implants by laparoscopic laser vaporization or excision by sharp dissection may or may not relieve the pain [2-5]. Unfortunately if surgical therapy provides palliation, it frequently is only temporary. Nevertheless, it is not clear how removal of one small implant can relieve pain.

Sometimes, the use of progesterone or estrogen suppression can relieve pain [6]. A naïve concept is that this type of therapy somehow "melts away" the endometrial implants and that relieve the pain. However, usually the pain, if relieved by these therapies, quickly returns once stopping the therapy. It is unlikely that "lesions that have melted away" will grow back immediately.

There have been several case reports and series finding one of the most effective therapies for the various types of pelvic pain, even those related to certain specific times of the menstrual cycle is dextroamphetamine sulfate [7-9]. One theory is that the pelvic pain is related to having increased cellular permeability either related to intrinsic defects on a genetic basis or acquired following some type of

injury. The increased permeability allows absorption of unwanted chemicals into the tissues leading to inflammation and pain. Because of hormonal changes during the menstrual cycle, these tissues may become more permeable [8].

Another factor that may play a role in the increased tissue permeability is hypofunction of the sympathetic nervous system. One of the functions of the sympathetic nervous system is to inhibit cellular permeability [10, 11]. A variety of chronic refractory illnesses which frequently are associated with pain, but not limited to pain syndromes, respond quickly and effectively to sympathomimetic amine therapy, especially dextroamphetamine sulfate [10,11]. It is believed that this drug stimulates an increase in the neurotransmitter for the sympathetic nervous system, dopamine [11].

One of the other conditions that seems to be exacerbated by sympathetic nervous system hypofunction is Crohn's disease which can present with pain but also with very frequent episodes of diarrhea. There have been reports of dramatic improvement of severe pain and diarrhea from Crohn's disease that had been refractory to standard therapy including adalimumab following treatment with dextroamphetamine sulfate [12].

The case described herein supports the concept that tissue permeability and sympathetic nervous system hypofunction may link a wide variety of chronic conditions that generally

respond very well to treatment with sympathomimetic amines especially dextroamphetamine sulfate. This case, however, also supports the concept that hormonal changes during the menstrual cycle may have an effect on tissue permeability, but it may not be limited to pelvic tissues.

Case Report

A 39-year-old woman with a six-month history of primary infertility sought help. She had regular menses with 29-day intervals. She had mild cramps which started when menses began. Her past medical history was significant only in having been diagnosed with Crohn's disease five years before. Her Crohn's disease manifested mostly as frequent daily diarrhea without dyschezia. Her symptoms eventually showed marked improvement after treatment with adalimumab. Her diarrhea was reduced to just one day per month which occurred at the periovulatory time. It was however, quite severe with 15-16 bowel movements per day which forced her to be home bound on that day. When she had daily diarrhea prior to adalimumab treatment, this one day was always the worst day. She had been advised by her gastroenterologist that adalimumab is relatively safe during pregnancy but there is still not a vast experience. However, pregnancy sometimes can cause Crohn's to go into remission and thus she may be able to stop the medication. At her initial consult she was explained that dextroamphetamine sulfate has been used not only to treat Crohn's disease but can be used to improve embryo implantation by inhibiting absorption of toxic material into the endometrium and improve implantation [13]. Furthermore there are enough data to establish the safety of pharmacologic dosages of amphetamines even when taken during the first trimester [14, 15]. She decided to start amphetamines salts 15-mg extended release capsules once daily. She continued the adalimumab. Because of normal semen analysis, normal post-coital, and because she attained a mature follicle and demonstrated oocyte release, she was treated exclusively with progesterone vaginal suppositories 200 mg twice daily. She conceived on her second cycle of therapy and has delivered a live full-term baby. The patient stated that over the last two years while her Crohn's was under reasonable control, there was not one month where she did not have the one day of severe incapacitating diarrhea at mid-cycle. Her first ovulation occurred about a month after starting the amphetamine salts and she did not have the one day of severe periovulatory diarrhea in either of the two cycles of treatment prior to her conception.

Discussion

If the present woman had severe dysmenorrhea or Mittelschmerz, most physicians would consider that she probably has endometriosis with implants on the bowel. However, she only had mild dysmenorrhea, no premenstrual component, no Mittelschmerz, and no dysmenorrhea. Thus, no symptoms of endometriosis and no evidence of it on pelvic exam or sonography. The fact that even when she had daily diarrhea before adalimumab therapy she still had this one day at mid-cycle as her worst day, supports the hypothesis that hormonal changes at mid-cycle can allow increased permeability allowing chemicals to enter the bowel and cause diarrhea. The fact that sympathomimetic amine therapy immediately corrected the problem when adalimumab failed emphasizes that relative sympathetic nervous system hypofunction compounds the problem. The fact

that she developed severe diarrhea for the one periovulatory day but not premenstrual may suggest that hormonal changes at this time allow maximum tissue permeability even more than the premenstrual time. Alternatively, another possible mechanism is that periovulation hormonal changes impair sympathetic nervous system function and this in turn increases tissue permeability allowing absorption of unwanted chemicals and toxic material leading to pathophysiologic events.

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