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ORIGINAL ARTICLE

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The "neurologic hypothesis": a new concept in the pathogenesis of the endometriosis?

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Abstract To cartograph the retroperitoneal infiltration of deep-infiltrating endometriosis of the rectovaginal space, we report on 467 patients who underwent laparoscopic/vaginal surgery for deep-infiltrating adenomyosis of the rectovaginal space. Exact localisation of the locoregional extension and of secondary infiltrating localisation where noted. The cervix and the rectovaginal ligament were mostly involved, while isolated lesions of the rectovaginal space were very rare. Comparisons of the most involved sites show an absolute correlation with the anatomical repartition of the pelvic sympathetic nervous system. We postulate a new "neurologic theory" which could be one more explanation for the development of adenomyosis of the rectovaginal space and maybe the peritoneum.

Keywords Endometriosis · Laparoscopic-vaginal surgery · Sympathetic nerve system

Introduction

Adenomyosis behaves retroperitoneally like a tumor and can affect various retroperitoneal structures. It remains unclear why and with which mechanisms this endometriosis infiltrates the retroperitoneum. The aim of our work was to establish an invasion pattern of the retroperitoneum.

Material and methods

We present a study of all of our patients on whom we performed radical surgery for adenomyosis of the rectovaginal septum since 1997. All of the surgical procedures began with a rectovaginal examination of the patient. Particular attention was paid to the estimation of involvement/stenosis of the rectum and involvement of the pelvic wall during rectal palpation. When the vagina was involved, the nodule was first dissected on the vaginal route and followed by laparoscopy. When the vagina was determined free of disease during palpation, the procedure began directly with a laparoscopy. A minute inspection of the entire abdominal cavity and of the pelvis was performed. When there was retroperitoneal infiltration or rectosigmoid infiltration, the retroperitoneal route was primarily chosen, and the exact depth and side/area of infiltration was documented. Our technique of deep anterior rectum resection/anastomosis has been previously described [1]. Directly after the procedure, infiltration and the side of the infiltration of the following sites were documented:

- Cervix
- Vagina
- Pouch of Douglas
- Inferior hypogastric plexus right/left (rectovaginal ligament)
- Ilio- and ischio-coccegeus muscles right/left
- Sacral plexus and/or sciatic nerve right/left
- Vascular part of the cardinal ligament right/left (from the uterine arteria to the medial rectal artery)
- Neural part of the cardinal ligament right/left (Nervi splanchnici pelvini)
- Ureter right/left

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– Rectum (mesenterial/antimesenterial)
– Sigmoid (mesenterial/antimesenterial)
– Ileo-coecum/appendix
– Bladder-wall
– Others

All these data were registered prospectively using Excel (Microsoft, Redmond, WA, USA).

Results

Since December 1997 we have performed radical laparoscopic or laparoscopic-assisted vaginal surgery for deep-infiltrating endometriosis of the rectovaginal space on 467 consecutive patients. All surgical procedures were performed by the author himself, originally at the Department of Gynecology at the University of Jena and since 2001 at the Women's Hospital at the University of Cologne. All procedures were performed laparoscopically except for one patient with extended infiltration of the anterior abdominal wall where a laparotomy was required. Table 1 shows the intraoperative data and the different surgical procedures.

Isolated infiltration of the rectovaginal space without infiltration of the Douglas pouch and/or the rectovaginal ligaments and/or the cervix was found in only three patients (0.6%). In all other patients (99.4%), infiltration of the posterior cervix and at least one rectovaginal ligament at its insertion at the cervix was found. We never observed a single lesion of the rectovaginal space with infiltration of the Douglas pouch without involvement of at least one of the rectovaginal ligaments. When the rectovaginal ligaments were infiltrated, both sides were involved in 266 patients (57%), only on the right side in 70 patients (15%) and only on the left side in 128 patients (27.4%).

Ureteral involvement/stenosis was found in 29 patients. In one patient this ureteral lesion was found isolated at the level of its crossing with the left common iliac artery, while in all other patients the ureter was involved in a conglomerate lesion at the level of the cross between the ureter itself and the uterine artery. The ureteral involvement was found on the left side in 27 patients and on both sides in one patient. One further patient presented with an isolated ureteral stenosis on the right side, but in her anamnesis, ureteral resection/anastomosis on the left side was relevant.

Extension to the neural part of the cardinal ligament (*Nervi splanchnici pelvini*) was found in 31 patients, 17 on the left side and 14 on the right side. No bilateral infiltration was observed at this level.

Resection of a part of the iliococcygeus and/or ischiococcygeus muscles was required on 32 patients (11 on the left and 21 on the right). Infiltration of the sciatic nerve itself was found on the right side in five patients and on the left side in two further patients.

Deep and extended infiltration of the rectum with rectal stenosis was found in 151 patients. In 17 of these patients, associated infiltration of the sigmoid was observed, while in three further patients, isolated stenosis of the sigmoid without rectal infiltration was found.

No isolated mesial infiltration of the bowel was found. In three patients with rectum infiltration, an associated extended infiltration of the ileocoecum was noted and required a double intestinal resection. Isolated involvement of the appendix was only found in four patients.

In patients where an anterior rectum resection/anastomosis was performed, no recurrence in the rectovaginal space, in both rectovaginal ligaments or in the vagina has been observed to date. Where an isolated resection of a nodule of the rectovaginal space was performed but without enlarged resection of both rectovaginal ligaments, 33 patients presented with a recurrence at the level of the rectovaginal ligament or of the upper part of the vagina.

Table 1 Operative data ($n = 467$)

	Data
Mean age (years)	26.3
Number of previous surgeries (average)	6.5
Operative time (average)	
With bowel resection	169.4 min
Without bowel resection	125.3 min
Bloodtransfusion (n)	$n = 4$
Further laparoscopic procedures	
Bladder-resection	$n = 22$
Ureter-resection/anastomosis	$n = 2$
Ureter-resection/ureterocystoneostomy	$n = 15$
Rectum-resection/anastomosis	$n = 151$
Sigmoide-resection/anastomosis	$n = 3$
Hemicolectomy/anastomosis	$n = 1$
Coecum-resection/ileoascendostomy	$n = 3$
Hysterectomy	$n = 6$

Discussion

When we consider the frequency of infiltration in the different sites, the cervix was nearly always involved, while a single lesion isolated to the rectovaginal space was very rare. It seems that the adenomyosis of the rectovaginal space is due more to an invasion coming from the cervix—like a "benign cancer" of the cervix—than a coelomic metaplasia directly in the rectovaginal space [2]. The endometriosis may grow and progress through direct extension and first infiltrates along the rectovaginal ligament. From there the disease is able to leave the rectovaginal ligament—statistically more frequently on the left side—and extend:

– Medially to the rectovaginal space and from there cranially to the Douglas pouch, ventrally to the vagina and dorsally to the rectum.
– Laterally/cranially along the uterine artery to the pars vasculosa of the cardinal ligament and consequently to the ureter (mostly on the left side)
– Laterally/caudally to the pelvic wall and the sacral plexus

– Dorsally to the rectum at its lateroanterior face

When we compare the cartography of the most frequent infiltration sites of the retroperitoneal adenomyosis with the topographic anatomy of the pelvic sympathetic nerves, we discover that both are identical:

– The cervix: the distribution of autonomous nerves in the genital organs is more extensive in the proximal vagina and the uterine cervical myometrium than in the uterus itself and is quite exclusively of a sympathetic type [3–5].
– The rectovaginal ligament: the s.c. sacrouterine ligaments are in fact not ligaments but the inferior hypogastric plexus itself. At this level—cervix and upper third of the vagina—this plexus contains sympathetic fibres exclusively.
– The upper part of the vagina: most of the nerves that join the vagina from the inferior hypogastric plexus enter its dorsal and middle parts. No nerves of macroscopic size can be traced from this plexus to the caudal part of the vagina [6].
– The trigonom of the bladder: the invasion coming from the anterior part of the cervix mostly involves the upper part of the trigonom where the sympathetic nerves enter the bladder.
– Parametry along the uterine artery: from the plexus pelvicus, sympathetic nerves are expanded laterally along the uterine artery to the terminal ureter [6] and to the lateral peritoneum of the ovarian fossa
– The ventrolateral portion of the rectum: sympathetic nerves coming from the pelvic plexus enter the rectum at its' anterolateral part.

Thus it seems that a correlation exists between the anatomical site of the pelvic sympathetic nerves and the infiltrating endometriosis. There could be two different hypotheses to explain this correlation. The first could be a neurotropism of the endometriosis for the sympathetic nerves. In this theory, the endometriosis should expand along the pelvic nerves, and the particular localisation of endometriosis on the cervix, the upper vagina and the rectovaginal ligaments could be due to the higher concentration of sympathetic nerves in these anatomical structures.

The second explanation could be that the sympathetic nerves play a direct role in the local development of the endometriosis. In reviewing the literature of the sympathetic nervous system, we found that the entire peritoneal pelvic cavity as well as the pelvic organs including the uterine vasculature are innervated by several subpopulations of sympathetic nerves [7, 8] but there are two particularities for the pelvic sympathetic innervation:

1. The first particularity is that in contrast to other parts of the peripheral nervous system, the uterine adrenergic innervation is highly influenced by endocrine factors (e.g. sex steroids) [9]. It was shown that the level of norepinephrine transmitter varies during the oestrous cycle [10]. Even more pronounced are the changes seen during the course of pregnancy, when the adrenergic nerves in the fetus-containing uterine horn undergo structural degeneration which is almost complete at term pregnancy; during the puerperal period, this adrenergic transmitter synthesis increases very slowly over the following months [11]. Thus, the uterus is able to alter its state of innervation through a hormonally controlled variation in the production of such neurotropic material essential for the maintenance or growth of a normal innervation. This phenomenon is of great importance because it is well known that endometriosis is decreasing or disappearing during the pregnancy while the level of oestrogen is increasing: It may be hypothesized that this decreasing of the endometriotic activity during the pregnancy and the puerperal period is directly the consequence not of the hormonal situation but of the disapparition of this uterine adrenergic transmitter synthesis. This is further in agreement with the observation that ovariectomy, which reduces the weight of the cervix and the uterine horns, also reduces total organ adrenergic transmitter synthesis [12]. On these grounds it may be further hypothesised that if this reduction of adrenergic activity should be able to reduce the local endometriotic activity, in controversy the increasing of this activity could be responsible for the development and/or growth of the endometriosis. Such a phenomenon is well known from the adaptation doctrine of Selye who has shown that the sympathetic activity could increase under external influence like that of the stress and could play a real role in psychophysiological aspects of tumor development [13]. Why the development of the endometriosis is mostly show on the cervix could be explained by two histologic particularities of this anatomical region: the first is that a very rich network of sympathetic adrenergic nerves innervate blood vessels as well as the cervical myometrium immediately beneath the epithelium. The second particularity is that during the mens, at the junction between the uterine endocrine and the cervical squamous cell epithel, superficial epithel cells are freed from their basal attachment. This is of importance because these endocrine cells are still alive and have the ability to infiltrate and proliferate deep in the cervix. It is our second hypothesis that changes in the synthesis, release, or proliferation of uterine adrenergic transmitter induced by humoral and/or local factors could influence the proliferation of these cells in the cervix ending in the formation of endometriosis.
2. The second particularity is that two of the subtypes of the pelvic sympathetic nerves—the s.c. neuropeptide-Y autonomous (NPY) nerves and the vasoactive intestinal polypeptide (VIP) nerves—show a particular localisation for the cervix, the rectovaginal ligament and the upper vagina—where we have mostly found the infiltrating endometriosis [14–16]. This is of importance because these autonomic nerves, espe-

cially the NPY nerves, are one of the most powerful angiogenic factors in the body and are involved in the neoangiogenesis of the pelvic organ: they are able to cause vascular smooth muscle cell proliferation and the stimulation of endothelial cell adhesion to matrix, migration, proliferation, capillary tube formation on matrigel and aortic sprouting [17]. Thus the angiogenic effect of the NPY and VIP nerves could be directly involved in the growth of endometriosis as angiogenic factors are able to establish, grow and invade endometriotic implants [18] especially in the pronounced stage IV [19–21].

Thus it is our theory that the sympathetic nervous system is directly involved in the establishment and growth of the endometriosis.

As a consequence we postulate that interference with the local pelvic sympathetic innervation—as in the pregnancy—may constitute novel therapeutic opportunities for the prevention, amelioration or treatment of pelvic endometriosis. In comparison to antiangiogenic compounds alone which are being tested as therapeutic agents in the treatment of endometriosis [22, 23], control of the local sympathetic nervous system should present one more approach: the direct control of the sensation of pain and dyspareunia by stopping the transport of sensitive information to the spinal cord and consequently to the central nervous system [24].

Different methods of control on the local sympathetic nervous system should be possible, one of which is the surgical transection of these nerves. In our study, radical surgery on extended lesions with bowel resection—where normally the risk of recurrence appears to be higher than in small localised lesions—showed better results in terms of recurrence than in localised resection of smaller lesions: in both situations we had excised the lesion with a histologically proven free margin but in situations where there was extended endometriosis of the rectovaginal space with rectum infiltration, resection of both rectovaginal ligaments and the upper part of the dorsal vaginal fornix was systematically required and performed while in smaller lesions only a reducing resection of the inferior hypogastric plexus was required. Thus in this radical surgery, the lowest rate of local recurrence could be explained by the higher bilateral destruction of the local vascularisation and of the cervicovaginal autonomous sympathetic innervation (inferior hypogastric plexus).

This neural theory could be extended to other localisations of endometriosis since this adrenergic pelvic innervation is also derived from the prevertebral and paravertebral ganglia via the hypogastric nerves—sigmoidal localisation for endometriotic implants—as well as via nerves running in the suspensory ligament to the tubal ends of the uterine horns—ovarial, tubal and peritoneal endometriosis of the fossa ovarica [25].

Our ''neural theory'' and its therapeutical implications have to be confirmed by fundamental studies in the laboratory.

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