Current Understanding of Anal Fissure Pathophysiology

MARIUSZ HENRYK MADALINSKI
Gastroenterology Department
The Princes Alexandra Hospital
Hamstel Road, Harlow, Essex CM20 1QX
U.K.
m.h.madalinski@pro.onet.pl

Abstract: - The etiology and pathogenesis of anal fissure (AF) is one of the most common causes of severe anal pain yet has never been fully understood. Factors which predispose people to developing AF include diarrhea, constipation, childbirth, medication as well as constant saddle vibration (amongst professional mountain-bikers) and using a jet of water from a bidet-toilet. For many years, it has been generally accepted that a sphincterotomy, whether surgical or pharmacologic, treats chronic AF because it produces a reduction in anal pressure, reverses sphincter spasms, and promotes fissure healing. However, recent studies cast doubt upon this explanation. A new theory explains that AF healing depends on biochemical processes in the anal passage. Eruption of tissues in the fissure region during defecation releases platelet products such as ADP, ATP, 5-HT, platelet activation factor, thrombin and substance P which cause the contraction of smooth muscles (of Internal Anal Sphicter and vessels) and result in difficulties in AF healing. The effect of a sphincterotomy is to reduce sphincter trauma during defecation and the consequent release of these potent smooth muscle contractors. An injection of botulinum toxin is thought to release the blockage in glyceryl trinitrate bioactivation in smooth muscle cells and suppress basal continuous sympathetic activity, resulting in AF healing.

Key-Words: - anal fissure, sphincterotomy, botulinum toxin, ischaemia, anal pressure, anal sphincters, Rho-kinase

1 Introduction

Anal fissure (AF) is one of the most common causes of a severe anal pain, but its exact incidence is unknown [1, 2, 3, 4]. Patients suffering from AF make up 10-15% of proctological consultations and it affects all age groups with an equal incidence in both sexes [5]. Despite this, its etiology, pathogenesis and the reason why a fissure frequently does not heal remains unclear. Also poorly understood are the predilection of AF to be localized in the posterior or anterior anal midline and the observed lack of granulation tissue at the fissure base [1-7].

2 What is Anal Fissure and what causes it?

2.1 Definition of anal fissure

An AF is a linear, longitudinal tear or ulcer extending below the dentate line to the margin of the anus. Only about 10% of women (compared to 1% of men) develop an anterior AF [1-4]. Fissure may be classified as acute or chronic and primary or secondary. In general, in 6 - 8 weeks, an acute AF, which looks like a crack in the skin, can become chronic. A chronic AF is characterized by indurated edges caused by the exposure of anal sphincter fibers. This occurs because chronic anal fissures are wider and deeper than acute fissures. Sentinel tags (pile) and hypertrophied papilla may complete the picture of a chronic AF [1-6].

2.2 The etiology and pathogenesis of anal fissure

On average, 235,000 new cases of anal fissure are reported every year in the USA and about 40% of them persist for months or years [8]. The primary cause seems to be trauma of the anal canal, although only 25% patients with chronic AF have constipation [1-4]. Constant saddle vibration in professional mountain bikers can lead to microtrauma and chronic inflammation which may result in anal fissure [9].

It is believed that the water stream in a bidet-toilet could be a cause of anterior fissure-in-ano [10]. 3-11% of anal fissures are associated with childbirth. Usually this type of etiology also predisposes to localization in the anterior anal commissure [7]. The link between sexual abuse and AF is not yet known [5].

Diarrhea has been found to be a predisposing factor in about 6% patients [1, 3]. Due to this reason, anal fissure may also be a consequence of bariatric procedure in obese patients [11].

Severe, painful anal ulceration (or ulcerations) after therapy with nicorandil have been observed for the past several years (since 2002) [12]. This potassium-channel activator, with adjunct nitrate effect, used in the treatment of severe ischaemic heart disease may also

cause other cutaneous ulcerations and oral ulcerations. The size of anal ulcers which occur due to treatment with nicorandil varies and they have undermined edges like chronic AF [13].

2.3 Pathophysiology of anal fissure

It has been generally accepted that hypertonicity of the internal anal sphincter (IAS) was involved in the pathogenesis of anal fissure. This opinion has been substantiated by a highly successful surgical treatment for anal fissure - internal sphincterotomy which generally results in a reduction of resting anal pressure [1-6].

Mucosal ischaemia has also been hypothesized to result in the non-healing of AF and progression of an acute anal fissure to a chronic fissure. Shouten *et al*. assessed microvascular perfusion of the anoderm by laser Doppler flowmetry and demonstrated significantly lower anodermal blood flow at the fissure site than at the posterior anal commissure of the controls [14]. They also showed that IAS resting pressure was inversely related to the blood flow at the posterior midline and blood supply was significantly lower at the posterior midline than anywhere else in the anal canal in healthy individuals [14, 15].

Postmortem angiographic studies performed by Klosterhalfen *et al*. showed no intramural collaterals between the branches of the inferior rectal artery in the anal canal wall and revealed an area of potential midline ischaemia in the internal anal sphincter [16].

For many years these facts complemented one another and created very logical theory which substantiated a pathomechanism of AF and formed the basis for anal fissure therapy. This notion has been quoted in nearly all articles concerning AF [1-8].

This common and thoroughgoing conviction about AF has been unshakable despite the fact that tailored anal sphicterectomy has very high healing rate and that another highly successful therapeutic procedure - anal advancement flap - can heal anal fissures without reducing maximum anal resting pressure [17, 18].

A lot of medication applied for topical therapy of anal fissure causes IAS relaxation. Because it mimics surgical sphincterotomy, this process is called pharmacological (or chemical) sphincterotomy. It may be performed with botulinum toxin (BTX) injections or the topical application of ointments such as calcium blockers, nitic oxide donors, a potassium channel agonist (minoxidil), inhibitors of angiotensin-converting enzyme, phosphodiesterase inhibitors, cholinomimetic (bethanechol) and an alfa-adrenoreceptor antagonist (indoramin) [19].

All these medications used topically or orally reduce anal resting pressures in patients with AF. Indoramine, for example, was found to reduce anal resting pressure by an average of 35.8% among patients with anal fissure. However, in double-blind randomized trials, despite significant reductions in anal resting pressure, a satisfactory effect in fissure healing was not observed [20].

Since 2005 there has been more evidence which has shown that we should verify our point of view for pathogenesis and healing of anal fissure [21, 22]. A study performed by Thornton *et al.* showed no correlation between fissure healing or deterioration in continence and subsequent significant reduction in maximum anal resting pressure (it fell by only 17%) [23].

Moreover, another recent study made by Ho and Ho showed that anal fissure healing is not dependent on the level of the mean of resting anal pressure [24]. Subsequent studies by Pascual *et al.* found no statistically significant differences between healing and non-healing of chronic AF after lateral internal sphincterotomy when comparing manometric and endosonographic findings [25].

3 A New Approach - Chemical Point of View for Anal Fissure Healing

There were attempts to have a look at anal fissure from the angle of biochemistry [3, 15, 26]. Generally these attempts concerned AF origin. One focus was on endothelial cell dysfunction associated with reduced synthesis of nitric oxide. The cause of this may be damage of endothelial cells, possibly due to antibodies [3, 27]. Antibodies were found in patients with chronic AF, but the group of investigated patients with AF was not sufficiently large to support this hypothesis.

Another theory is that IAS is hypersensitive to beta 2 agonists and therefore the pathogenesis of AF was sought in psychological stress. It also produces a sustained tonic raise in anal pressure [15, 26]. Moreover, stress may cause molecular changes in beta 1 adrenergic receptors [28]. The postulated mechanism may precede development of AF and may be also caused by anorectal infection. A conception of infectious etiology of AF was known many years ago. One of the precursors of this thinking was Nesselrod [29]. This raises the question of whether AF is a form (or stage) of anorectal infection.

I would like to present the first chemical theory which strives to explain the therapy results of different types of AF. One of them is anal fissure associated with anal sphincter hypertonicity. In 2002, Minguez et al. reported that 30% of anal fissures occur with a low to normal anal sphincter pressure [30]. Therefore it was crucial to bring together both theory and prior knowledge and bear in mind the studies by Minguez et al.[30]. The foundations of this theory are as follows:

-Acknowledge poor anal sphincters "stretchability", chemical medatiors of inflammation and relationships between these elements as the main cause of difficulties in anal fissure healing.
-Reduction of anal pressure is a consequence of pharmacological or surgical therapy for AF and is no prerequisite for AF healing.

If the stretchiness of the anal sphincters is poor, eruption of tissues in the fissure region during every defecation causes the platelet products such as adenosine diphosphate (ADP), adenosine triphosphate (ATP), 5-hydroxytryptamine (5-HT), platelet activation factor, as well as thrombin and substance P, cause contraction of smooth muscles (of IAS and vessels) resulting in problems in the healing of AF due to ischaemia. When the endothelium is not traumatized, then these substances cause relaxation of normal blood vessels by releasing NO and prostacyclin I_2 (PGI_2) [31,32, 33].

The regenerating tissues in the AF region are a place where there is diminished production of NO (particularly in response to serotonin and agonists of α2-adrenergic receptors) and microvascular damage activates haemostatic processes. Fibre formation followed by cortical actin accumulation and cell rounding is stimulated by thrombin in endothelial cells [34].

Thrombin-stimulated endothelial cell contraction may be abolished by inhibition of RhoA by *Clostridium botulinum* C3 exoenzyme [34]. Also the inhibition of Rho by *Clostridium botulinum* C3 exoenzyme reverses hypoxia induced by a decrease in eNOS expression [35]. Therefore the hypothesis suggests that RhoA is also relevant to successful pharmacologic sphincterotomy.

The most successful pharmacological sphincterotomy is therapy with BTX [3, 19]. There is a common knowledge that BTX is an endopolypeptidase produced by the anaerobic bacterium *Clostridium botulinum* and acts presynaptically by blocking acetylcholine released at the neuromuscular junction thereby reducing the myogenic tone [36]. However, the exact mechanism of BTX on anal sphincters is incompletely understood [37]. Studies by Lindsay *et al*. [38] suggest that BTX may directly inhibit the release of neurotransmitters from adrenergic nerves. This pathway is especially important because activation of α2-adrenergic receptors induce activation of Rho-GTP, which activates Rho kinase. It phosphorylates the myosin-binding subunit of MLC phosphatase and inhibits its activity and thus leads to muscle contraction [39, 40, 41].

We may suppose that when we decrease adrenergic activation by BTX application into internal anal sphinter (or external anal sphincter), we will diminish concentration of noradrenaline – an agonist of numerous G protein-coupled receptors, and diminish activation of RhoA [19]. It is especially important for contracted IAS because prolonged smooth muscle contraction may be understood by remodelling or cytoskeletal rearrangement related to activity of the RhoA/Rho kinase signaling [39, 40,41]. Moreover, chronic NOS inhibition enhances α2-adrenoreceptor-stimulated RhoA and Rho kinase *in vitro* [40].

Bacterial toxins can induce contraction of endothelial cells *via* the Rho/Rho-kinase pathway as a result of myosine light chain phosphorylation [42]. It is very probable that inflammation or other causes described in part about the etiology of AF could lead to chronic contraction of the anal sphincter. It may possibly lead to local hypoxia which has an influence on endothelial nitric synthase (eNOS) expression. As a result, the mechanisms described in this article may be triggered and lead to AF [19].

Madalinski *et al.* reported patients with chronic AF, who did not respond to initial GTN topical treatment, nor showed any improvement after injection of BTX type A, but showed considerable improvement after repeated administration of GTN [43, 44]. Therefore a suggestion that application of BTX releases the blockage in GTN bioactivation in smooth muscle cells and suppresses basal continuous sympathetic activity, causing modulation of the anal sphincter is a reasonable conjecture. This effect is probably responsible for chronic AF healing [19].

May be we should also change our mind regarding a higher anal pressure. We used to think that a higher anal pressure is peculiar to increased tension of IAS. This theory took into account one more known fact that isometric muscle contraction manifests itself in difficulties in muscle distention.

Presented in the light of the studies by Thornton *et al.*, Pascual *et al*, and Ho and Ho, this theory acquires another significance [23, 24, 25]. It places a particular emphasis on anal stretchability and biochemical processes and was published in February 2005. Two months later, Ho and Ho published their study which supported this theory [24, 32]. Later that year (in July), Thorton *et al.* published their observations and in 2007 the work of Pasqual *et al.* was published [23, 25].

Recently, this theory has been supported by others to explain difficulties in healing of anal fissures after surgery [45]. Other doctors quoting this theory concede that reducing trauma of defecation may play an important role for AF healing and have created a new device – posterior perineal support. It brings a significant improvement in the symptoms of patients with AF [46].

The further studies concerning BTX and the small GTPase Rho may be significant not only for the therapy of AF, but also for atherosclerosis and heart diseases; because the same reactions are believed to play an

important role in these conditions [19]. Overexpression of RhoC correlates in various human cancers with high metastatic ability and poor prognosis, therefore the described interdependences may be attractive for different specialities [47].

4 Conclusion

The recent studies suggest that we should modify the traditional point of view on fissure healing. The described biochemical theory explains that the effect of sphincterotomy is to reducing anal trauma associated with defecation and the consequent release of potent smooth muscle constrictors. The hypothesis assumes that RhoA is relevant to successful pharmacologic sphincterotomy. The results of further studies concerning the described biochemical theory may have much wider implications that just therapy for AF.

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