Etiopathogenic Theories of Idiopathic Megacolon

Subjects: Archaeology

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Idiopathic megacolon is a condition characterized by an enlarged colon and aperistaltic syndrome in the absence of a detectable cause. The main symptom is considered chronic constipation, refractory to drug treatment and without surgical indication. IM affects both sexes and the symptoms develop early in childhood or in adulthood.

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1. Etiopathogenic Theories

The pathogenesis of the disease is still controversial, although a number of hypotheses are already documented. The highlighting of some HP and IHC changes on the resection specimens compared to the healthy control population, showed a rather varied lesional heterogeneity, making it difficult to invoke, in terms of etiopathogenic importance, the greater or lesser responsibility of any of the identified factors. Associated or not, the decreased cellularity of nerve plexuses [1][2], alterations of extramural spinal innervation [3], neuromuscular disorders [4], and decreased number of Cajal cells [5], are not described as possible causes. Unfortunately, one thing seems very clear to us: immunohistochemical studies (IHC) are not consistent in supporting any of these hypotheses [6][7], discovering new and possible changes as an etiopathogenic source. Attentively, we understand that there is a damage at the parietal colonic level, but who generates it, what mechanisms determine these changes, and what is the target population group, if there is one, are questions to which we do not have a clear answer but only speculations. A good example is the invocation of events and lesions described in children with aperistaltic megacolon, in which the absence of tendon membranes from the myenteric plexus is detected as well as alterations (quasi-complete atrophy) of the tendon fiber network in the muscle [8][9][10]. These lesions were later described in adults, thus leaving open the possibility of detection and other changes related to the causality of the presence of the megacolon.

2. Cajal Cells

Changes in Cajal interstitial cell numbers are described in patients with idiopathic megacolon or chronic constipation by numerous studies and suggested as an etiopathogenic basis [11][12][13][14][15][16][17]. They are considered a true intestinal pacemaker (“little brain” at the enteral level); however, starting from the premise that their number decreases physiologically with age anyway and by the fact that a number of other communications do

not confirm their involvement in the etiopathogenesis of idiopathic megacolon, this theory remains for the moment only a new subject of controversy [1].

3. Smooth Muscle Cells

Another theory suggests that the development of the idiopathic megacolon is based on degenerative changes in smooth muscle tissue [13][18]. The alteration of colonic muscle cells in the case of idiopathic megacolon in cats [19][20], and similar changes identified in mice [21], are also documented. In corollary, a 2006 study in patients with idiopathic megacolon showed a reduction in colonic smooth cell myofilaments and an altered expression of the pattern of myosin-type muscle markers with heavy chain or histone deacetylase 8, despite the normal histological appearance of standard hematoxylin-eosin staining. [22].

4. Intramural Tendon Fiber Network

It is considered that three elements are essential for normal motility: smooth muscles, the intramural connective tendon network, and the integrity of the myenteric plexuses [10]. In IM, atrophy of the tendon network causes the disappearance of peristalsis completely [2] and allows uncontrolled dilation of the colon [23]. The functional consequences of the atrophy of the tendon structures at the level of its own muscle become obvious if we consider the investigations carried out by Rollo et al. [24], who showed that peristalsis is entirely dependent on the integrity of this network. During the contraction of the longitudinal muscle fibers, the tendon network modulates the dilation of the layer of uncontracted circular muscles. At the same time, the tendon network does not allow the elongation of the relaxed longitudinal fibers during the contraction of the circular muscular layer. Both phenomena that alternate in the colonic motor activity are thus dependent on the integrity of the tendon network, being coordinated by the enteric nerve plexuses and determined by the propulsion of the colonic content [1].

It appears extremely interesting that, in IM, aperistaltic syndrome is not accompanied by colonic wall hypertrophy. Moreover, it even describes colonic parietal atrophy in cases of idiopathic megacolon, especially in the longitudinal muscles.

On the other hand, it is known that both smooth muscle cells and collagen elements have a mesenchymal origin. This explains why smooth muscle cells synthesize type I and III collagen [25][26][27][28][29][30]. *Growth factor beta-1* induces collagen synthesis in smooth muscle cell cultures [30]. This supports the hypothesis of a defect in the synthesis of collagen in smooth, genetically determined muscles, which underlies the appearance of idiopathic megacolon, especially in young individuals. In support of this hypothesis, a colonic perforation is reported in a patient with a form of Ehlers-Danlos syndrome with a significant defect in type III collagen synthesis [24]. Colon dilatation phenomena have also been described in patients with other pathologies related to altered connective tissue metabolism, such as scleroderma or amyloidosis [31][32][33][34].

Moreover, the network of tendon fibers in the muscles is particularly rich in type III collagen fibers. It has a relatively high metabolism of hydroxyproline compared to type I collagen. As an important consequence, the production of

type III collagen is affected in ascorbate deficiency, as documented in tissue culture experiments [26][27].

5. Pelvic-Perineal Muscle Disorders

Some studies show pelvic-perineal muscle disorders of up to 40% in patients with megacolon. Controversy arises as to whether these disorders are part of the initial systemic neuromuscular disorders, a consequence of colonic atony, or a cause of colonic distension. Rectal distension, as found in pelvic-perineal muscle disorders, inhibits colonic tonicity through a negative feedback mechanism mediated by a viscero-visceral reflex [35]. Patients with chronic constipation, due to pelvic-perineal muscle disorders, also have an inadequate postprandial colonic motor response [36]. The aspects are with direct therapeutic involvement. In the absence of a correction of these pelvic-perineal dysfunctions, a subtotal colectomy with ileorectal anastomosis will not improve the symptoms related to the slowed digestive transit [37][38][39].

6. Genetic Appearance

Many of the functional and morphological changes in colonic smooth muscle tissue, interstitial structures, and nerve structures, were detected in mice during the overexpression of the Hoxa-4 gene [40]. It encodes a specific transcription factor that modulates cell positional identity [41]. In mice with an overexpressed Hoxa-4 gene, a short segment with aganglionosis in the terminal colon was detected. Moreover, the lymph nodes present in the longitudinal muscles were malpositioned. In individuals with significant impairment, death occurs early postnatal. In the case of a less severe impairment, survival to adulthood may be recorded. These data suggest that the idiopathic megacolon may be caused by genetic changes involving the distribution and interaction of different cellular components in the colonic wall. At the same time, the involvement of extrinsic factors (diet, pharmacological substances) can be considered [42] as associated mechanisms.

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