Embryological development of the anorectal malformations. Hypothesis

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Abstract

Currently, there is no hypothesis to explain the embryological development of anorectal malformations (ARMs). Those assumptions that are described in the literature contradict scientific facts and should be rejected as untenable. A hypothesis is described based on the indisputable fact that with ARMs the anus is always absent. Evidence is provided that with visible and invisible ARMs there is always a functioning anal canal. Except for the true cloaca, the cause of the pathology is the lack of development of the ectodermal anlage of the anal canal. The internal anal sphincter (IAS) moves inside the endodermal rudiment of the anal canal, but without meeting the ectodermal part on its way, it moves anteriorly and upward. By this time, the anal canal has already been created up to the subcutaneous layer above the anal fossa. Outside the rudiments of the anal canal, the IAS creates narrow and rigid fistulas. They are short when penetrating inside the subcutaneous portion of the external anal sphincter (anal stenosis), with perineal, vestibular, urethral, and vaginal ARMs. But they can be long, opening under the scrotum, as well as in some vaginal fistulas, which without reason are called persistent cloaca. From this hypothesis it follows that all ARMs, except for the true cloaca, have a functioning anal canal and are therefore low types of ARMs. This hypothesis is offered for scientific testing. Evidence-based discussions is important to improve our understanding of the etiology, pathophysiology, and effective treatment of children with ARMs.

Keywords: anorectal malformations; embryology; anal canal ectopy; persistent cloaca; hypothesis.

1. Introduction

A knowledge of embryology is crucial for understanding anorectal malformations (ARMs) [1]. As for the embryology of ARM, there are more different assumptions than scientific facts. The embryologist Kluth so identified the state of this problem: "Today, the normal and abnormal development of the hindgut is still a matter of speculation" [2]. His research findings indicate that "(1) the embryonic cloaca never passes through a stage that is like any form of anorectal malformation in neonates, including the so-called "cloacas" in female embryos, and (2) to explain abnormal development, studies in abnormal embryos are mandatory" [2]. The following are indisputable scientific facts of the embryological development of anorectum.

I.1. Indisputable scientific facts of the embryological development of anorectum

1.1.1. The genitourinary septum descent and separates the cloaca into two channels: the rectum posteriorly, and the bladder and the urethra (urethra and vagina in the woman) anteriorly [3,4].

1.1.2. Immediately after separating cloaca, the internal anal sphincter (IAS) is located away from its intended site in the ectoderm (perineum). “Normally, in the post cloacal period, the endodermal internal anal sphincter migrates in the craniocaudal direction to meet with the ectodermal portion” [5]. It is about the unique ability of IAS to create a channel in the tissues of the perineum (self-creation).

1.1.3. The anal canal divides into superior and inferior parts. The superior two-thirds are derived from the endoderm and are lined by simple columnar epithelial cells. The inferior one-third is derived from ectoderm and is lined by stratified squamous epithelial cells. The junction that delineates these two epithelia is called the pectinate line or the dentate line [1,2,3,6].

1.1.4. During the 10th week, the anal tubercules, a pair of ectodermal swellings around the proctodeal pit, fuse dorsally to form a horseshoe-shaped structure and anteriorly to create the perineal body [4]. It follows from this that the formation of the distal ectodermal part of the IAS begins from the perineum and is formed by migration upward, to the meeting with the endodermal part of the IAS.

1.1.5. These unconditionally reliable data allow us to conclude that ARM may occur during two periods of embryological development of the fetus. (1) During the formation of the cloaca, when further development of the anorectum stops and a cloaca is formed, as in birds and reptiles. In these cases, the bladder, uterus, and rectum empty into a wide cavity called the cloaca. They do not have a urethra, vagina, and anal canal. (2) In a later period, ARM occurs

because of the cessation of development of the exogenous part of the anal canal. This is evidenced by the absence of an anus in the anal fossa.

2. Regularities of pathological anatomy and physiologists of ARMs.

2.1. All ARMs are characterized by the absence of the anus inside the subcutaneous portion of the external anal sphincter (EAS). Obviously, this is evidence about a violation of the formation of the ectodermal part of the anal canal.

2.2. All fistulas are in the projection of the central sagittal plane. They are always displaced forward and up from where the anus is usually located.

2.3. In cases of visible (perineal and vestibular) fistulas they slightly displaced up from the anal dimple. Upward displacement increases in varying degrees in cases of invisible fistulas.

2.4. In all cases of visible (perineal and vestibular) fistulas, there is a normally functioning anal canal, as evidenced by X-ray and manometric studies [7], and by the good results of cutback procedure that does not damage the anal canal [8].

These postulates are discussed in detail below.

3. Radiological studies at ARM

3.1. ARM with visible fistula. On x-ray examination at the rest, the anal canal is in constant contraction, as in normal, preventing leakage of feces **(Figure 1a, c).** Its length is equal to the length of the normal anal canal in accordance with the age of the child. During bowel movements, the anal canal opens wide, as in normal, to reduce resistance to passage of feces **(Figure 1b).** When examined with a Foley catheter, the balloon inflated in the rectum easily penetrates the anal canal and is retained over a narrow, rigid fistula, which varies in length from 2 to 4 mm, depending on the age of the child (**Figure 1. d, e, f)**. It depends on the thickness of the skin and subcutaneous tissue.

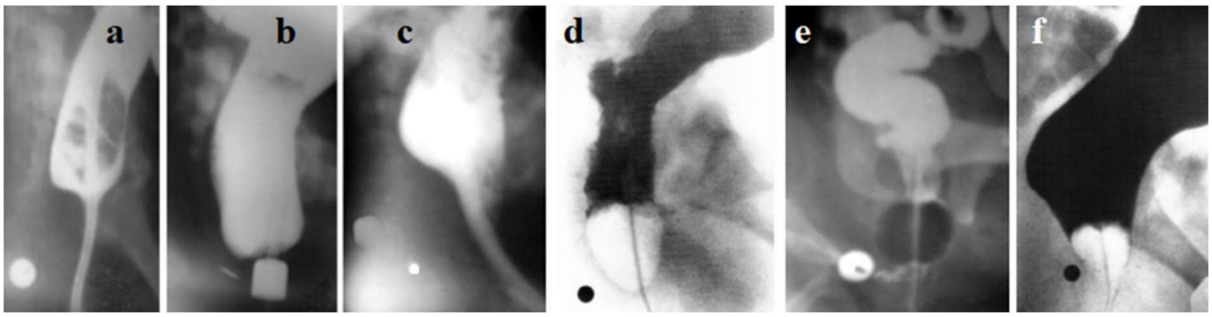

Figure 1. Lateral radiographs of anorectum in patients with ARMs with visible fistulas. **(a-b)** Pictures of the same child taken at different times. **(a)** A catheter was inserted from the vestibular fistula into the rectum to contrast the intestine. At rest, the anal canal is contracted around the catheter. **(b)** On reexamination, an attempt to defecate with a wide opening of the anal canal was fixed. The distance between the button in the anal dimple and the wall of the opened anal canal is 4 mm. **(c)** During the administration of barium, relaxation of the IAS occurred, because of which barium penetrated the upper part of the anal canal in front of the rectal tube. At this moment, the posterior wall of the anal canal is pressed against the rectal tube by the contracted PRM. This is an X-ray manifestation of the rectoanal inhibitory reflex. The IAS is fixed to the rigid ring through which it penetrates outward. **(d, e, f)** When the anal canal is opened, the distance from the wall of the anal canal to the marker in the anal dimple ranges from 2 to 4 mm, depending on the patient's age [7].

Thus, in X-ray examination of patients with visible fistulas, a functioning anal canal was always determined, which differed from the normal anal canal only in that it lacked a distal section 2-4 mm long, which is normally surrounded by the subcutaneous portion of the EAS. The anal canal opened with a narrow rigid fistula in front of the anal dimple on the perineum or in the vestibule. The presence of a normally functioning anal canal is confirmed by a manometric study. The basal anal pressure and the rectoanal inhibitory reflex did not differ from the normal anal canal [7,9].

3.2. ARMs with long perineal fistula. The endodermal portion of the IAS in the perineal tissue forms normally. However, once it reaches the subcutaneous tissue, it creates a narrow channel. It can be short if the IAS penetrates the subcutaneous tissue and skin not far from the anal dimple (**see Figure 1**), or very long if it passes under the skin and penetrates outward at the root of the scrotum (**Figure 2)** [10].

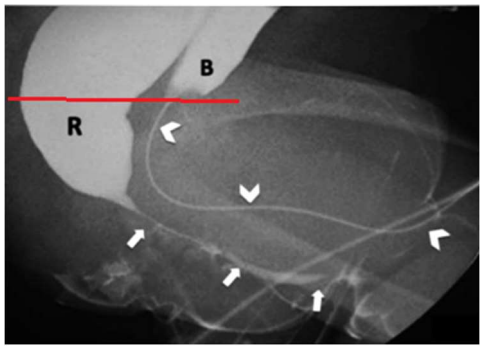

Figure 2. Sfoungaris et al presented the case of a male neonate with imperforate anus and a fistula exiting on the penile skin. "Colostogram and urethrography. Course of recto-penoscrotal

fistula (arrows) and urethra (arrowheads). R: rectum, B: urinary bladder" (caption from article) [10].

I conducted a pubococcygeal line (red). The distal part of the intestine, designated by the authors as the rectum, is the anal canal. We see a long and narrow fistula running under the skin from the already formed anal canal to the root of the scrotum. This typical case shows that BAC penetrating tissues beyond its natural path creates a narrow, rigid fistula, the length of which depends on the distance between the anal canal and the point of entry into any cavity or outward. This means that the BAC first reaches the subcutaneous tissue opposite the anal fossa and, without meeting the ectodermal rudiment coming towards it, turns forward and moves until it penetrates some cavity.

The studies described above coincide with the recent statement of pediatric surgeons (ARM-Net Consortium): - “According to present knowledge, the “fistula” in ARM represents an ectopic anal canal and should be preserved as far as possible to improve the chance for fecal continence” [11]. As can be seen from this definition, the authors do not limit ectopia of the anal canal only to visible fistulas, which is confirmed in both manometric and radiological studies [12].

3.3. ARMs with visible fistula. In most cases of ARM without visible fistulas (without fistula, and with urethral and vaginal fistulas), there is a normally functioning anal canal, as evidenced by X-ray [8] **(Figure 3**), manometric studies [13], and the results of operations that do not damage the anal canal [8]. As shown in the article by Huange et al, the urethral fistula was located 1 cm above the anal edge [14], i.e., the fistula connected the urethra not to the rectum, but to the anal canal.

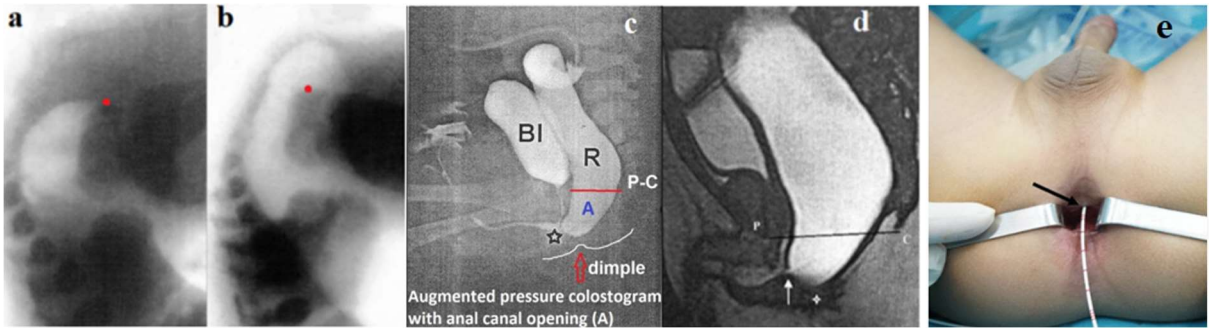

Figure 3. Studies of ARMs without visible fistula. (a, b) Radiographs were taken in the newborn without visible fistula in a horizontal position: (a) before and (b) during abdominal compression. The red dot shows the caudal contour of the ischium. During the abdominal

compression, the anal canal opened completely, because of which the gas approached the skin of the perineum. (c, d) Augmented-pressure distal colostograms (c-X-ray), (d-MRI). In both cases, under the influence of very high pressure, the anal canal opened, and its caudal wall approached the anal dimple. (e). The urethral fistula (arrow) was located 1 cm above the anal edge without obvious scar" (from the article by Huang et al) [14].

Thus, the short fistula in ARMs without visible fistula is displaced from the anal dimple higher than with visible fistulas. However, by the time of displacement the anal canal is already formed, and its blind ending also is at 2-4 mm from the anal dimple. Since ARMs with urethral fistulas and without fistulas have a normally formed anal canal, they are low types. Kraus et al confirm the above facts: - "It is extremely important in this regard to understand that the lowest part of the rectum is usually collapsed from the muscle tone of the funnel-like striated muscle mechanism that surrounds the rectum in 90% of cases…" [15]. Unfortunately, the interpretation of surgical observations is incorrect, since it is known from anatomy that there are no muscles around the rectum at all. The muscles, that compress the intestine, and thus prevent the leakage of intestinal contents located around the anal canal. Since the authors do not cite any studies, so the 90% figure should be treated with caution.

From the above data, it follows that IAS is involved in the formation of the anal canal up achievements the subcutaneous tissue. It can penetrate out through the ring of the subcutaneous portion of the EAS. However, such penetration is always accompanied by the formation of stenosis. This is how congenital anal stenosis occurs. More often, IAS moves anteriorly and upward, leaving behind a functioning anal canal **(Figure 4).**

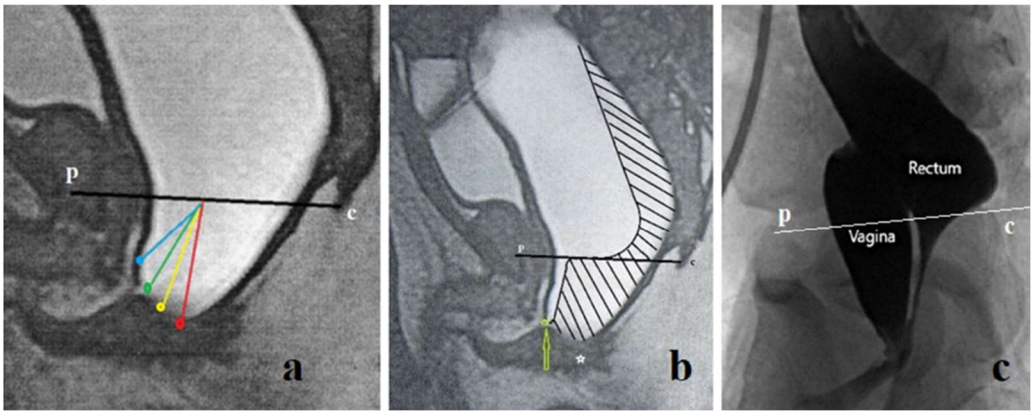

Figure 4. (a) Scheme of the occurrence of different variants of ARMs in males, depending on the degree of displacement of the IAS upward: red - the normal location of the anus (congenital anal stenosis - CAS); yellow - perineal fistula; green - bulbar fistula; blue - prostatic

fistula. During bowel movements, the anal canal opens wide. **(b)** At rest, the anal canal contracts. **(c)** In a female with low vaginal fistula the rectum is not dilated. The contrast agent injected through the colostomy passes through the anal canal and flows out of the vagina in a wide stream.

The anal canal is fixed in the place where it penetrates any cavity (**Figure 4 a**). And therefore, at rest, when it is in a contracted state, it is far from the anal dimple and cannot be found during surgery through a wound in the EAS ring (**Figure 4b**). Since the place of attachment is closer to the rectum than normal, the length of the closed anal canal is shorter than the age norm. However, during defecation, the levator plates stretch the walls of the anal canal, bringing its distal wall closer to the anal dimple (**Figure 4 a**). Therefore, during defecation, the length of the anal canal from the pubococcygeal line to the marker in the anal dimple is equal to the length of the normal anal canal. Based on the analysis of the literature, it can be assumed that almost all ARMs, except for the true cloaca, have a functioning anal canal, i.e., are low types of defects. I was unable to find in the literature a radiological study for bladder neck fistula. To determine exactly whether ARM with bladder neck fistula are high anomalies, more research is needed with high rectal pressure provocation.

4. Cloaca

4.1. The true cloaca. From an embryological point of view, “Persistent Cloaca is a rare condition that occurs only in female infants. It results from the total failure of the urorectal septum to descend, and therefore occurs at a very early stage of development (10- mm stage)” [4]. This is an example of atavism, when development stops at the stage that is characteristic of birds and reptiles. It is characterized by confluence of the rectum, vagina, and bladder in a urogenital sinus. Therefore, the urethra, vagina and anal canal are completely absent in them.

4.2. The so-called "persistent cloaca"

The malformation first described by Hendren [16] did not meet the definition of a cloaca at all, because the patients had a urethra and a vagina. Hendren did not perform any studies to determine the function of the urinary system and did not have a clear idea of the pathological anatomy of the defect. So, for example, he believed that hydrocolpos appears because of vaginal distension with urine. For example, he wrote: - “Intermittent catheterization of the bladder and/or urine-filled vagina can often provide adequate decompression” [17]. This idea was picked up by Peña. Neither he nor his colleagues conducted studies on the state of the urinary system. Their articles do not contain references to such studies by other authors [18].

Lacking any scientific basis, Peña proposed surgical treatment as if it were a true cloaca, i.e., ignoring the presence of the urethra, vagina, and anal canal [19]. First, the presence of the urethra, vagina, and anal canal indicates that the cloacal membrane has already divided the cloaca into the urogenital sinus and intestine. And there is no way for them to reunite into a single channel. Secondly, in a study by Runck et al the molecular pathologies in cloaca malformation were defined. "Cloaca malformation is also defined as ‘persistent cloaca’ because it is thought that it might result from an arrest of the division of the embryonic cloaca. However, our results using the Shh knockout mice show that the epithelium from the common channel has matured and does not show the same characteristics as a cloaca epithelium before septation..." [20]. Thus, the samples were taken by pediatric surgeons from the "common canal" turned out to be more mature than in the case of an undivided cloaca, i.e., from the point of view of embryology, the “persistent cloaca” is not a cloaca.

Although from the point of view of embryology and pathological physiology, these cases correspond to the anal canal ectopy into the vagina, they differ from the above case (see Figure 4c). The so-called "common channel" does not correspond to the idea of normal vagina, since its lumen is narrow, and the walls are rigid. Sagittal MRI **(Figure 5 d)** shows separate exits of the urethra, vagina, and anal canal. Thus, the authors without reason designate the lower part of the vagina by the common channel (CC) [21]. In some cases, the upper part of the vagina is sharply expanded over the stenosis (hydrocolpos). The abovementioned patterns of movement of the IAS make it possible to explain the occurrence of such variants of vaginal fistulas. **(Figure 5).**

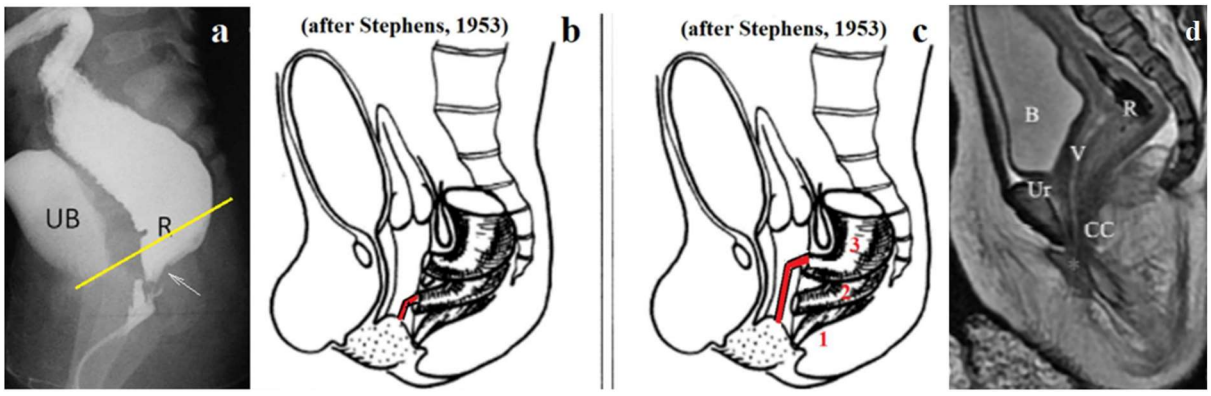

Figure 5. Variants of an ARMs with fistulas in the vagina. (a) The contrast agent injected into the rectum (R) penetrates the narrow, uneven channel. There is no contrast between the vagina and bladder (UB) and rectum. The sigmoid colon is narrow, indicating low rectal pressure. The caudal part of the intestine is located below the pubococcygeal line. The arrow shows the

concavity created by the contracted puborectalis muscle. The urethra is not visible, as it is in a contracted state, as is normal. (b-c) On the diagram of the location of fistulas in girls, proposed by Stephens (1-vestibular; 2- vaginal low; 3-vaginal high), I have drawn a channel by a red line that was creates by an IAS in the vagina, in cases, when an internal cavity has not yet arisen. (d). A case described as "persistent cloaca" by Lin et al with the caption: - «. Sagittal MRI of the lower abdomen showed the rectum (R), vagina (V), uterus (Ut), bladder (B), urethra (Ur), and ill-defined common channel (CC)» [21]. The cross-section shows a normal-length urethra with an external opening in the vulva. The vagina appears to be a narrow fistula, and there are no signs of a common channel. This is a typical picture of a vaginal fistula with an unusually narrow canal in the vagina.

All vaginal fistulas form in the post-cloacal period, when the IAS, having reached the subcutaneous tissue opposite the anal fossa, and without meeting the ectodermal part of the anal canal, continued to migrate forward and upward. The anterior displacement of the anus always occurs exactly in the projection of the sagittal plane. Not a single observation has been described of IAS passing past the urethra. In females, the fistula cannot penetrate the urethra since the vagina is in its path. In cases where IAS penetrates the vaginal cavity, a typical vaginal fistula occurs (**see Figure 4 c)**. My hypothesis on the assumption of the assumption that during the formation of the ARMs, in most cases the internal channel in the vagina has not yet formed. Therefore, IAS behaves in the same way as in males with a long and narrow subcutaneous fistula that opens under the scrotum. It forms a narrow and rigid fistula in the center of the vagina, which in some cases blocks the exit from the proximal vagina. In such cases, a hydrocolpos develops. This canal can be short if the BAC has penetrated the lower vagina **(Figure 5. b),** or long **(Figure 5. c).** Secondly, as shown in **Figure 5**, a patient with a so-called cloaca has a functioning anal canal, since the upper part of the anal is located caudally to the pubococcygeal line. Due to the relaxation of the IAS, the contrast agent penetrated the upper part of the anal canal. At this time, the contracted puborectalis muscle (together with the EAS) closed the lower part of the anal canal. This is a typical X-ray manifestation of the rectoanal inhibitory reflex.

4.3. Conclusion. Analysis of the literature convinces that high ectopic anus in females inevitably leads to the formation of two types of vaginal fistulas. Upon penetration into the vaginal cavity, a short rigid canal is formed in its wall. If the vaginal cavity has not yet formed, then a long, rigid fistula is formed, which opens in the vulva. The fistula can be of different sizes, depending on the height of the IAS penetration. That defect, which the authors without

any evidence called persistent cloaca, is an ectopia of the anus in the vagina and they, like all ARM with ectopia, have a normally functioning bladder and urethra. Some pediatric surgeons have noticed that urological problems occur after correction of the urogenital sinus and are absent if the surgeons solved only the rectal problem. It has been suggested that severe complications of the urinary system are due to surgery, and not congenital pathology [22, 23]. The above data suggest that with anal ectopia in the vagina, there is a normally functioning anal canal, regardless of the height of penetration and the presence of vaginal constriction. To identify the anal canal and preserve it during surgery, it is necessary to create high rectal pressure.

5. Hypothesis of embryological development of ARM.

5.1. Currently, there is no hypothesis to explain the embryological development of ARMs. Those assumptions that are described in the literature contradict scientific facts and should be rejected as untenable.

5.2. Of all the ARMs that are given in the classifications, only true cloaca occurs because of a violation of the development of the cloaca.

5.3. All other types develop in the post-cloacal period, when successful division of the cloaca has already occurred to create the urethra, vagina, and anal canal. In the absence of concomitant urological pathology, the bladder, urethra, and vagina develop as normal. At the first stage, the IAS, inside the endodermal part of the anal canal, descends in the tissues of the perineum towards the ectodermal rudiment. For an unknown (probably genetic) reason, the ectodermal primordium is not activated and does not create the distal part of the anal canal, as evidenced by the absence of the anus.

5.4. The internal anal sphincter can create an elastic canal within the embryonic rudiments. Outside the embryonic rudiments, it creates a narrow, rigid canal, usually until it opens into some cavity (urethra, vagina) or out through the skin.

5.5. By the time the IAS reaches the subcutaneous tissue opposite the anal dimple, it is located within the deep and superficial portions of the external anal sphincter, as well as in the loop of the puborectalis muscle and within the levator plates.

5.5.1. In rare cases, when the IAS penetrates the ring of the subcutaneous portion of the EAS, a narrow, rigid fistula forms “congenital anal stenosis.” This name is not sufficiently accurate, since it does not differentiate stenosis of the anal canal and anus. In 1978, J. Caffey wrote in

his book that pediatric surgeons continue to habitually call the ectopic anal canal a fistula [24]. This ambiguity played a cruel joke in the future, after Peña began to consider the anal canal a fistula, which most pediatric surgeons still destroy [15]. Therefore, I propose to call this anomaly “Congenital stenosis of the anus.”

5.5.2. Most often, the IAS, without meeting the ectodermal rudiment of the anal canal, moves forward and upward. In males, it can penetrate the perineum in front of the anal dimple, creating perineal ectopy, and then urethral (bulbar, prostatic and bladder-neck) ectopy. In females: perineal, vestibular, and vaginal ectopy. The IAS is fixed at the site of penetration, away from the anal fossa to the fibrous ring. However, during defecation, its distal wall approaches the anal fossa at 2-4 mm, depending on the age and thickness of the skin and subcutaneous tissue. Therefore, in the closed state, the length of the contracted IAS is shorter, the higher its attachment [25]. However, the length of the open anal canal corresponds to the age norm [7]. Secondly, since the closed anal canal is displaced anteriorly, its relationship with the pelvic muscles differs from the norm, which does not significantly affect the function of the anal canal [7, 12].

5.5.3. Vaginal ectopia may be low or high. In addition, it can manifest itself as a sharp narrowing of the vagina, which is caused by the penetration of IAS into the vagina, in which a cavity has not yet formed. In these patients, the function of the urinary system and anal canal is not impaired. There is no evidence to the contrary. This pathology has nothing to do with the cloaca. Terrible post-operative results are a consequence of unnecessary operations.

I propose this hypothesis for scientific testing. Evidence-based debate is important to improve our understanding of the etiology, pathophysiology, and treatment of children with anorectal malformations.

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