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Obliteration of the Processus Vaginalis After Testicular Descent

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The testis develops in the abdominal cavity and descends into the scrotum. Although numerous theories have been proposed, the mechanism of descent and the reason for its inhibition remain unknown. Furthermore, none of the explanations account for the other occurrences related to the descent, such as failed obliteration of the processus vaginalis, or the reasons for the decrease in fertility and increase in the risk of malignancy associated with an undescended testis. The gubernaculum is a primitive mesenchymal tissue that was first described in 1786. However, the role of the gubernaculum in the descent process remains obscure. The testis descends through the processus vaginalis. Although the processus vaginalis (PV) is usually defined as a simple peritoneal protrusion, it actively develops into the gubernaculum. The gubernaculum gives rise to the smooth muscles that surround the processus vaginalis. The striated cremaster muscle (CM) is also derived from the gubernaculum. Because the testis descends through the processus vaginalis, the muscles develop to propel the testis. After propelling the testis, the smooth muscle (SM) undergoes programmed cell death. The initiation of programmed cell death through the intrinsic pathway requires activation of phospholipase C. A transient shift in the autonomic balance via a decrease in the sympathetic tonus and an increase in the parasympathetic tonus is essential for initiating this programmed cell death. Programmed cell death in the SM is the physiological pathway for the obliteration of the processus vaginalis. Differences in the timing, intensity, or duration of this physiological pathway result in pathological conditions. A shift before testicular descent diminishes the SM content that is required to propel the testis, and thus inhibits descent. The early shift persists throughout childhood and results in the decrease in fertility and increase in the risk of malignancy because of the differences in signal transduction. Despite a successful descent, persistence of the shift alters the contractility of the CM by increasing the cytosolic calcium levels. Contracted CMs retracts or even ascends the testis. Inadequate intensity or duration of the shift of autonomic tonus causes failure of the programmed cell death. Persistence of the SM hinders the obliteration of PV and gives rise to hydroceles or inguinal hernias depending on the amount of residual smooth muscles. Similar findings from different countries support these explanations. Thus, our proposed mechanism satisfactorily explains the process of descent while considering all the factors related to the process of testicular descent.

Testes are initially located in the abdomen. They descend into the scrotum around the 28th week of gestation. Although several theories have been proposed over the centuries to explain the mechanism of descent, the subject remains debatable.[1]

Because the testes need to travel a distance to reach the scrotum, the descent requires a force. Therefore, a theory that describes the descent should explain the source of force and the mechanism of descent. The theory should also include the reason for the inhibition of descent. Undescended testes are associated with a decrease in fertility and an increase in the risk of malignancy. These occurrences have traditionally been explained by the influence of hyperthermia on the testes in the suprascrotal region. Operative treatment at an early age has been proposed over the years to shorten the time the testes are subjected to hyperthermia. However, treatment during the first year of life does not prevent fertility in 20-25% of the patients. Defective early postnatal gonadotropin surge has been used to explain the decrease infertility associated with undescended testis. Therefore, only surgical treatment is considered insufficient.[2] Performing a testis biopsy and administering gonadotropins in selected patients with undescended testis has been suggested to overcome the risks. In recent years, some authors who initially opposed early operation or hormone treatment because of the risk of testicular injury are now in support of it.[3,4] Recent study conclusions impression that the modern approach to the treatment of undescended tested is early surgical treatment, biopsy of the testis, and administering hormones. However, this approach may be associated with severe consequences, as previously reported by these authors. Furthermore, the cause and mechanism of the decrease in fertility and increase in the risk of malignancy remain

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unknown. The debate regarding the age and mode of treatment will continue until the exact cause and mechanism of descent inhibition is fully understood. Undescended testis is associated with a high incidence of epididymal-vasal anomalies. It may also be associated with hormonal alterations such as blunting in the response of luteinizing hormone to luteinizing hormone-releasing hormone and of testosterone to human chorionic gonadotropin. Testes that descended initially may subsequently retract and progress to acquired undescended testes. The descent carries a risk of intravaginal torsion that results in testicular atrophy. Furthermore, despite a normal descent, the processus vaginalis (PV) may not follow the physiologic pathway of obliteration and may give rise to an inguinal hernia or hydrocele.[5] Therefore, a theory that explains the descent should explain all these occurrences known to be related to the descent.

Herein, we have described the testicular descent through a new perspective, based on the findings of recent reports, which considers all associated or related conditions.

Gubernaculum and processus vaginalis during testicular descent

The gubernaculum is the most important structure that takes part in the testicular descent, and is at the center of several theories that explain the descent. It is a primitive mesenchymal tissue. Although it was first defined in 1786, the exact role of the gubernaculum during testicular descent and its fate remain unexplained.[1] The other important structure during testicular descent is the PV, which provides a path for the testes to descend. It was first described in 176 by Galen.[6] The PV is not a simple peritoneal protrusion as usually described; it actively develops into the gubernaculum (Figure 1).

We have previously confirmed the development of the striated cremaster muscle (CM) in the gubernaculum,[7] which has also been reported in other studies.[8-10] Although the CM is considered to represent projections of the internal oblique muscle, it has some distinguishing properties. It is a striated muscle that is not under voluntary control and is mostly composed of slow-twitch fibers.[11] Striated muscles with similar properties are also encountered in the esophagus and urethral sphincter. According to Patapoutian et al.,[12] the striated muscles of the esophagus transdifferentiates from the preceding smooth muscle (SM). A similar transdifferentiation has been demonstrated in the urethral sphincter.[13] However, no SM other than vascular SM has been encountered in the gubernaculum before the development of the CM. Satellite cells, which are a type of stem cell in striated muscles, originate from vascular SM.[14] The striated CM expresses α-SM actin. During the 22nd and 23rd weeks of gestation, both vascular SM and CM express MyoD. We have previously proposed that CM transdifferentiates from the vascular SM and that relaxin-like factor (Insl3) may play a role during myogenesis.[7] The findings of the study by Yuan et al.[15] support our hypothesis that this signaling pathway plays a role in myogenesis. The findings of the study by Botti et al.[16] support our hypothesis regarding the development of CM through transdifferentiation. The gubernaculum has also revealed myofibroblasts during the 22nd week of gestation, and SM that surrounds the PV appeared by the 27 weeks of age. Myofibroblasts represent a progression toward the development of SM. We have demonstrated that both SM and CM develop from the primitive mesenchymal tissue gubernaculum,[7] which is similar to the finding of the study by Youssef and Raslan.[17] The gubernaculum ceases to exist after the development of these muscles.

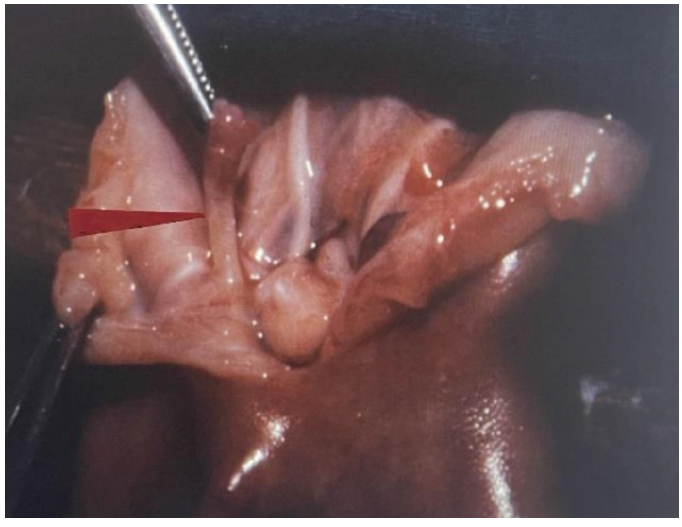

FIG. 1. The gubernaculum, the red arrow indicates the apertura of the processus vaginalis.

The muscles generate force, and the testes descend around the 28th week of gestation through the PV. Only one explanation seems possible for the presence of SM around the PV by the 27th week of gestation. It is propelling the testis.

Descent of the testis

Propulsion, like the passage of bolus through the esophagus, satisfactorily explains the descent of the testis. Propulsion also explains the risk of torsion during descent, which may subsequently vanish the testis.

Hutson has divided the descent process into phases. Furthermore, he proposed that the gubernaculum migrates to the scrotum during the second phase of the testicular descent under the control of calcitonin gene-related peptide (CGRP).[1] Because there is no remaining gubernaculum after myogenesis and before the descent, it cannot migrate during testicular descent. Hutson have erroneously reflected that we have reported the gubernaculum to respond to sympathetic autonomic fibers rather than CGRP.[18] However, our explanations have never contained such an explanation. They have reported that sympathetic nerves do not have a major role in controlling gubernacular migration to the scrotum.[19] According to them, our explanations also lack the control of direction of migration.[18] They have reported that sympathetic nerves do not play a major role in controlling gubernacular migration to the scrotum.[19] They reported that CGRP is the main neurotransmitter, and adrenergic agonists and antagonists have limited effects.[20] Furthermore, they believe that migration is the universally accepted prime mechanism. Because

we describe descent via propulsive activity, gubernacular migration under the guidance of CGRP or other neurotransmitters is not a part of our theories. The role of autonomic innervation is very clear in our theory. Furthermore, if CGRP is the most important neurotransmitter, an undescended testis should be associated with a decrease in the CGRP level. However, CM samples from boys with undescended testes demonstrate evidence of exposure to high CGRP levels.[21]

Fate of the processus vaginalis after testicular descent

Comparative evaluation of the peritoneum, obliterated PV, and sacs of patients with undescended testes, hydrocele, or inguinal hernia demonstrate striking differences based on the sex and the underlying disease.[5,22] The difference between them is the SM content. While the peritoneum and obliterated PV does not contain any SM, sacs associated with undescended testis, hydrocele, or inguinal hernia contain different amounts of SM. Sacs associated with female inguinal hernias also contain striated muscles, indicating that PV is a sexually dimorphic structure.[22] The SM content is reportedly the highest in sacs associated with inguinal hernias, followed by sacs associated with hydroceles. Sacs associated with undescended testes contain the least amount of SM.[5] In addition to SM, myofibroblasts have also been encountered in sacs. Myofibroblasts are more frequently detected in sacs associated with hernia than in those associated with hydroceles or undescended testes.[22,23] It appears that SM is a transient structure to propel the testis. It should disappear after completing its duty for the obliteration of PV only by leaving the dartos muscle around the tunica vaginalis.[5,22,23] The structures that complete their function disappear via programmed cell death. Dedifferentiation of SM into myofibroblasts appears to be a step toward programmed cell death. Mouravas et al.[24] have supported the necessity of programmed cell death in SM for obliteration (Figure 2).

The fibrous structure, the residual gubernaculum, which is located distal to an undescended testis and the round ligament in girls, is actually the obliterated PV.[25] Our reports that have revealed the inhibition of obliteration of PV by the persistence of SM have been confirmed in the literature by various authors.[26-29]

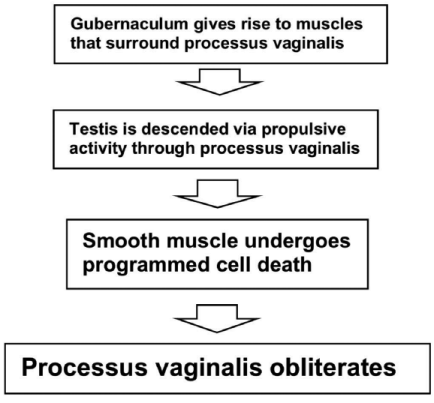

FIG. 2. The steps of the process of descent.

Differences found in smooth and striated muscles associated with undescended testis

Sacs associated with undescended testes contain more calcium than those associated with inguinal hernias or hydroceles.[30] SM associated with undescended testes differ from SM associated with inguinal hernias because of their lack of response against carbachol.[31] Neurotransmitters of the autonomic nervous system act through receptors coupled with G-proteins. In G-protein-linked signaling, a lower response indicates desensitization of the receptor resulting from more exposure to agonists.[32] The absence of a response to the muscarinic cholinergic agonist carbachol indicates that the SM associated with undescended testes has been exposed more to a parasympathetic tonus.

CM associated with undescended testes demonstrate angular fibers and group atrophy that is indicative of neurological damage via autonomic innervation.[33-37] Molinaro et al.[38] also demonstrated neurological damage in the CM associated with undescended testes.

Although CM associated with both descended and undescended testes reveal similar distribution based on fiber type, the diameter of type-2 fibers is smaller in boys with undescended testes than those with descended testes.[11] Preservation of the distribution of fiber types indicates that the lesion involves the autonomic nervous system. Sympathetic tonus is exerted through catecholamines via the beta-2 adrenergic receptors in the CM. Type-2 fibers are more responsive to beta-adrenergic stimulation.[39] Decrease in the diameters of type-2 fibers may indicate that they are exposed to less sympathetic tonus. These muscles demonstrate a greater response to the beta-adrenergic agonist isoprenaline. The greater response is evidence of the reduced exposure of CM to sympathetic tonus.[21]

The androgen effects on muscle depend on the fiber type.[40] Androgens enlarge type-2 fibers.[41] Thus, the decrease in the diameter of type-2 fibers indicates a decrease in the androgenic effects. The sympathetic system is also sexually dimorphic and depends on androgens.[42] Androgenic effects on striated muscles may be exerted through sympathetic tonus. However, it is also possible that both sympathetic tonus and androgens may act synergistically on CM. Therefore, the decrease in type-2 fibers indicates both a decrease in androgenic effects as well as a decrease in the sympathetic tonus in boys with undescended testes. More androgen receptor expression in CM associated with undescended testis reveals evidence of being subjected to less androgenic effects.[43]

Electron microscopic evaluation has revealed that the number of non-myelinated fibers decreases in peripheral nerves associated with undescended testes.[36] Evaluation of the cremasteric reflex via electromyography has excluded the presence of a defect in the afferent neurotransmission, indicating that the decrease in non-myelinated nerve fibers reflects a decrease in the number of sympathetic nerve fibers.[44] Persistent exposure to a reduced sympathetic tonus in boys with undescended testes appears to be associated with a decrease in the number of sympathetic fibers.

Sympathectomy increases the number of CGRP and substance P immunoreactive sensory fibers.[45] Because androgen receptors

are present in afferent fibers and absent in sympathetic fibers, the afferent system plays a role in the establishment of sexual dimorphism in the autonomic nervous system.[42] Evaluation of contractile responses against CGRP and substance P revealed a reduced response in CM associated with undescended testes. The reduced response indicates more exposure and is indirect evidence of the decrease in sympathetic tonus.[21]

CM associated with undescended testes have higher amplitudes of contraction than CM associated with inguinal hernias, which does not depend as much on calcium entry through voltage-gated calcium channels for generating a contraction.[21,46] Electron microscopic evaluation has also revealed contracted fibers and round and electron-dense mitochondria, indicating mitochondrial calcium overload, in CM associated with undescended testes.[36]

Increased contractility that does not depend entirely on calcium entry in addition to the presence of contracted fibers and mitochondria with calcium overload, indicate an increase in the levels of cytosolic calcium. However, the total calcium content is significantly low in CM associated with undescended testes.[47] Motor neuron-related complications are associated with an increase in the total calcium content. Thus, a decrease in total calcium content indicates that the disorder does not involve the motor neurons.[47] Despite an increase in cytosolic calcium, the low total calcium content can be attributed to the mobilization of calcium from internal stores. Stored calcium is released from the sarcoplasmic reticulum via ryanodine and/or inositol 1,4,5-trisphosphate-sensitive channels.[48] However, the evaluation failed to reveal any difference in the caffeine sensitivities of CM based on the location of the testes. Furthermore, it ruled out the role of ryanodine-sensitive channels in the increase in cytosolic calcium levels in boys with undescended testes. Because calcium influx into the cell is enhanced by beta-2 adrenergic agonists, which also activate the calcium pumps in the sarcoendoplasmic reticulum, the alterations in CM associated with undescended testes can partly be attributed to the decrease in the beta-2 adrenergic effect.[49,50] Inhibition of the sarcoendoplasmic reticulum calcium pumps and release of calcium from inositol 1,4,5-trisphosphate-sensitive stores require the generation of inositol 1,4,5-trisphosphate (IP3). IP3 is generated by activating phospholipase C. Phospholipase C is activated by the parasympathetic system. During IP3 generation, diacylglycerol, which activates protein kinase C, is also generated as a co-product. Protein kinase C inhibits calcium entry into the cell.[48] Thus, the decrease in the beta-adrenergic tonus and the increase in the parasympathetic tonus because of the protein kinase C-induced inhibition of calcium influx and the inositol 1,4,5-trisphosphate-induced inhibition of the sarcoplasmic reticulum calcium pumps explain the decrease in total calcium content and the increase in cytosolic calcium.[51] The smooth and striated muscles associated with undescended testes demonstrate a persistently low sympathetic tonus and an increased parasympathetic tonus that appears to be associated with a decrease in the number of sympathetic nerve fibers. Alterations in the autonomic tonus persist throughout childhood (Figure 3).[52]

Experimental support for inhibition of descent through the decrease in sympathetic tonus

Testicular descent can be inhibited by administering non-steroidal anti-androgens or performing a chemical sympathectomy during the 15th to 19th day of fetal life. The testicular location is associated with a reduced exposure to the sympathetic tonus, which is essential at a critical point of development for the descent of testes.[53,54]

Other suprascrotal locations, including retractile, gliding, and ascending testes

Terms such as gliding or retractile testes have been used for testes located in the suprascrotal region. However, a common etiology for suprascrotal localizations is possible. Evaluating the testicular location based on the different definitions and identifying the different etiologies may make the topic more confusing than understandable.

A retractile testis is one that in present in the suprascrotal region due to a hyperactive cremasteric reflex. However, the definition of a hyperactive cremasteric reflex remains obscure. Furthermore, an activated reflex arc cannot be reactivated before the completion of the ongoing reflex arc. Thus, if a testis retracts because of the cremasteric reflex, it should retract and descend alternatively. Moreover, the cremasteric reflex is subject to desensitization and cannot be reactivated repeatedly. Therefore, the cremasteric reflex cannot explain the suprascrotal localization of the testis.[55]

Electromyographic evaluation of the cremasteric reflex in boys with undescended and retractile testes has revealed similar findings.[44] A permanent decrease in the sympathetic tonus and an increase in the parasympathetic tonus increases the cytosolic calcium level in the CM which initiates CM contraction. The contractile status of the CM defines the degree of suprascrotal localization. A permanent increase in the contractile status may result in contracture formation. Contracture formation results in an ascending testis. Thus, the contractile status of the CM, and not the cremasteric reflex, defines the suprascrotal localization of an initially descended testis.

The alterations also link the decrease in fertility and increase in the risk of malignancy

Binding of ligands to beta-2 adrenergic receptors coupled to G-proteins releases αs, which activates adenyl cyclase to generate cyclic adenosine monophosphate. However, the parasympathetic system acts via the activation of phospholipase C.[56] An increase in the levels of cyclic adenosine monophosphate (cAMP) activates the transcription of specific target genes that contain the cAMP-

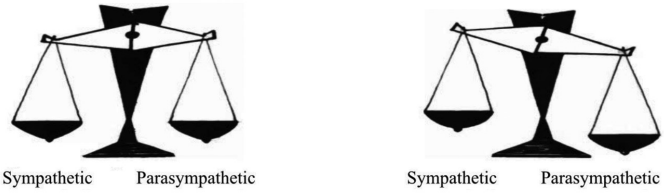

FIG. 3. The autonomic balance shifts in boys with undescended testis in favor of a parasympathetic tonus.

response element. Regulation of gene expression by cAMP plays an important role in controlling cell proliferation and differentiation.[48] The decrease in sympathetic tonus, and thus lower cAMP levels in boys with undescended testes, can be attributed for the decrease in spermatogenesis. A high risk of infertility (20-25%) among boys with undescended testes is associated with a reduction in the number of germ cells in both testes. For every 6 months of delay in orchiopexy, there is a 1% reduction in the paternity rate,[2] which can be attributed to the ongoing signals toward programmed cell death. However, relocating the suprascrotal testis into the scrotum will not normalize the shifted autonomic balance. The ideal temperature for the sympathetic tonus to produce an effect on the αS activity is approximately 36 °C. Adenyl cyclase is inhibited in testes that are subjected to high temperatures.[57,58] Therefore, the injury does not only result from the shift in autonomic balance. Additional factors may play a role in deepening the effect of the decrease in sympathetic tonus by inhibiting adenyl cyclase activity. Relocating the undescended testes into the scrotum may help alleviate the additional component of injury.

Continuous stimulation of the protein kinase C pathway by phorbol esters results in the development of tumors.[48] Dominance of a parasympathetic tonus results in an increase in the stimulation of the phospholipase C pathway, which may be attributed to the increase in the risk of in males with undescended testes.

Programmed cell death in smooth muscle

The principal component of programmed cell death is a proteolytic system that involves a family of proteases called caspases.[59] Caspases are activated through the following two main pathways: extrinsic and intrinsic. The extrinsic pathway involves the Fas and Fas-ligand systems. Although activation of this system directly executes programmed cell death in some cells, the involvement of mitochondria is essential in other cells. Involvement of the mitochondria which pertains to the depletion of calcium stores via the G-protein-linked signal transduction constitutes the intrinsic pathway.[59] Activation of phospholipase C, which generates diacylglycerol and IP3, is one of the initial steps. IP3 promotes the release of calcium from the internal stores.[60] Although depletion of calcium from the endoplasmic reticulum may play a role in programmed cell death, it can also be induced by a sustained increase in the cytosolic calcium levels.[61,62] The early increase in cytoplasmic calcium levels is followed by a delayed increase in mitochondrial calcium levels, which is a critical event in programmed cell death.[63] The increase in mitochondrial calcium facilitates calcium-induced transient opening of the mitochondrial permeability transition pores and the release of cytochrome c.[62] Precipitation of programmed cell death requires a state of calcium overload.[63] A set of proteins participate in the regulation of programmed cell death. Among these proteins, Bcl-2 inhibits apoptosis, and Bax induces apoptosis when overexpressed.[59] Bax is present in the cytosol but gets incorporated into the mitochondrial membrane after a death is signaled. It induces the opening of the permeability transition pore, release of cytochrome c, and activation of the downstream caspase pathways.[59] Apoptosis precipitation is associated with the overexpression of calcium ATPase in the sarcoendoplasmic reticulum, which augments cellular and sarcoendoplasmic calcium loading.[64]

Activation of phospholipase C in the SM is accomplished by parasympathetic tonus. Therefore, the autonomic balance shifts in favor of a parasympathetic tonus. The parasympathetic system does not depend much on androgens. Although the sympathetic system is sexually dimorphic and highly responsive to androgens, it lacks androgen receptors. Androgens affect the sympathetic system through the afferent system.[42] The increase in the parasympathetic tonus can be accomplished by decreasing the sympathetic tonus via the upregulation of androgen receptor-controlled afferent neurotransmitters.[21]

G-protein-linked signal transduction activates phospholipase C to generate IP3. Depletion of calcium stores and an increase in the cytosolic calcium is followed by an overload of the mitochondrial calcium. Increase in the Bax and Fas levels and regulated targeting of Bax initiates the cascade of programmed cell death (Figure 4).

The alterations in structures associated with undescended testes support the initiation of programmed cell death. The presence of undescended testes indicate a decrease in the SM necessary for propelling the testis through the PV via an early shift in the balance of autonomic tonus. Early activation also causes the shift to be sustained. The study findings of Beuermann et al.[65] confirm the role of programmed cell death in the mechanism of testicular descent.

Programmed cell death in smooth muscle explains vaso-epididymal anomalies

Undescended testes are associated with a decrease in the size of the efferent and epididymal ducts. The decrease in size mainly occurs due to the underdevelopment of the muscular wall. This may indicate that an undescended testis is a primary congenital illness of the testes and spermatic ducts that may not be completely reversible by surgical treatment.[66] Orchidectomy induces apoptosis in the epididymis.[67] Whereas, chemical sympathectomy causes SM abnormalities within the vas deferens. The muscle layer area and epithelial height in the vas deferens are also affected by sympathetic denervation.[68] Castration, even after puberty, decreases the volume of the vas deferens muscle.[42] Thus, the persistent decrease in sympathetic tonus may satisfactorily explain the development of

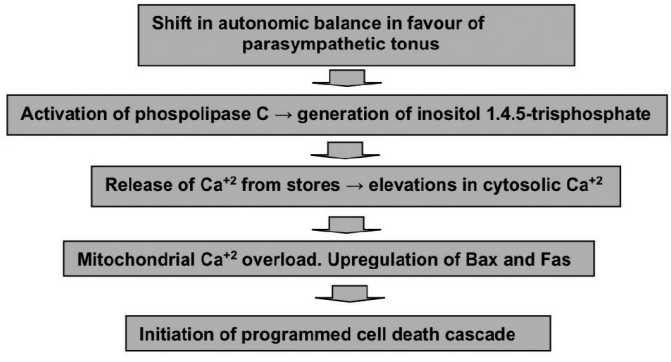

FIG. 4. Programmed cell death in the smooth muscle.

vaso-epididymal anomalies via programmed cell death in males with undescended testes.

Persistence of smooth muscle: reason and results

Histopathologic evaluations have revealed the presence of SM in sacs associated with inhibition of PV obliteration. Furthermore, tissue explants of sacs also predominantly give rise to SM.[69] Sympathetic nerves are among the factors that exert trophic changes in SMs by increasing the intracellular cAMP levels via the beta-adrenergic receptors.[70] Therefore, sympathetic innervation is necessary for the maintenance of SM.[71] The persistence of SM in the sacs indicated the maintenance of a autonomic tonus without a shift. The mechanism that initiates programmed cell death in the SM is the shift in the balance of the autonomic tonus in favor of a parasympathetic tonus (Figure 3). A shift that is achieved by a decrease in the sympathetic tonus over time or a change in the intensity or duration is a physiological requirement for the obliteration of the PV. Both early and inefficient shifts from this physiological phenomenon result in several pathological conditions (Figure 5).

The persistence of SM inhibits PV obliteration. The amount of residual SM determines whether an inguinal hernia or hydrocele develops.[72] The SM surrounding the PV may contribute to the increase in risk of incarceration in a child with an inguinal hernia. The pressure in sacs associated with hydroceles is usually higher than the intra-abdominal pressure.[73] The SM in the sac wall may contribute to the increase in pressure by pushing the fluid into the scrotum.

The close interaction between the regulation of autonomic tonus and control of pulsatile release of gonadotropins points the responsible center

Although controversial, boys with either a unilateral or bilateral undescended testes have decreased mean levels of plasma testosterone and luteinizing hormone.[74] Post-natal Leydig cell secretion is reduced in boys with undescended testes. Because chemical sympathectomy blocks androgen biosynthesis, blunting might be explained by a decrease in the sympathetic tonus.[75] Furthermore, because pituitary luteinizing hormone secretion is also defective, the disorder involves not only the testes but also the central nervous system.[76]

Peripheral regulation of adrenergic maturation is governed by suprasegmental mechanisms in the central nervous system.[77] Central catecholaminergic neurons are involved in sympathetic nerve discharge.[78] Its activity is within the center of regulation of shift in an autonomic tonus. Thus, silencing of the central catecholaminergic activity may shift the autonomic balance in favor of a parasympathetic tonus.

Various non-peptide neurotransmitters, including catecholamines, participate in the modulation of gonadotropin-releasing hormone neuron activity and gonadotropin-releasing hormone secretion.[79]

Central catecholaminergic activity also plays a role in the control of the pulsatile release of the gonadotropin-releasing hormone. A close interaction exists between the regulation and synthesis of androgens and the sympathetic tonus. Silencing of the central catecholaminergic activity may also be responsible for the hormonal alterations associated with undescended testes.

A center that takes part in the regulation of both the shift in autonomic balance and the androgens appears to be responsible for the process.

A unilateral undescended testis is actually a bilateral disease

Electrophysiological evaluation of the cremaster reflex in patients with undescended testes demonstrates a shortened latency and prolonged activity of cremasteric responses, which indicates impairment of the suprasegmental inhibition. Furthermore, the undescended and contralateral descended sides reveal similar results. On the other hand, 20-25% of malignancies associated with unilateral undescended testis are encountered in the scrotal testes.[80] The autonomic tonus balance is regulated in the brain, which demonstrates lateralization. The side of the clinical picture is determined through the lateralized localization of the centers. Despite the unilateral clinical appearance, both testes are affected.

Concluding remarks

Herein, we have defined the mechanism of testicular descent while taking into consideration all the variables associated with the descent process. Noteworthy points, such as the association between SM and inhibition of PV obliteration, have already been

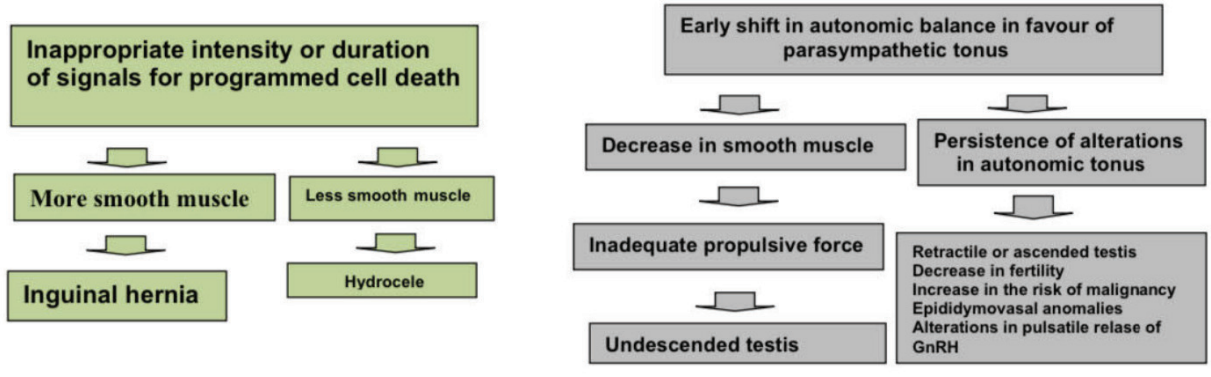

FIG. 5. Initiation of programmed cell death before the descent of testis or its inappropriate intensity and duration in different clinical problems.

confirmed in previous studies. We believe that this article provides the most satisfactory explanation proposed to date. Further studies are required that evaluate the mechanism of testicular descent from our perspective.

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REFERENCES

1. Heyns CF, Hutson JM. Historical review of theories on testicular descent. *J Urol*. 1995;153:754-767. [CrossRef]
2. Hildorf S, Clasen-Linde E, Cortes D, Fossum M, Thorup J. Fertility Potential is Compromised in 20% to 25% of Boys with Nonsyndromic Cryptorchidism despite Orchiopexy within the First Year of Life. *J Urol*. 2020;203:832-840. [CrossRef]
3. Cortes D, Thorup J, Visfeldt J. Hormonal treatment may harm the germ cells in 1 to 3-year-old boys with cryptorchidism. *J Urol*. 2000;163:1290-1292. [CrossRef]
4. Thorup J, Cortes D. Surgical Management of Undescended Testis - Timetable and Outcome: A Debate. *Sex Dev*. 2019;13:11-19. [CrossRef]
5. Tanyel FC, Dağdeviren A, Müftüoğlu S, Gürsoy MH, Yürüker S, Büyükpamukçu N. Inguinal hernia revisited through comparative evaluation of peritoneum, processus vaginalis, and sacs obtained from children with hernia, hydrocele, and undescended testis. *J Pediatr Surg*. 1999;34:552-555. [CrossRef]
6. Fourie N, Banieghbal B. Pediatric Hydrocele: A Comprehensive Review. *Clin Surg*. 2017;2:1448. [CrossRef]
7. Tanyel FC, Talim B, Atilla P, Müftüoğlu S, Kale G. Myogenesis within the human gubernaculum: histological and immunohistochemical evaluation. *Eur J Pediatr Surg*. 2005;15:175-179. [CrossRef]
8. Backhouse KM. Embryology of testicular descent and maldescent. *Urol Clin North Am*. 1982;9:315-325. [CrossRef]
9. Heyns CF. The gubernaculum during testicular descent in tvhe human fetus. *J Anat*. 1987;153:93-112. [CrossRef]
10. Tayakkanonta K. The Gubernaculum Testis And Its Nerve Supply. *Aust N Z J Surg*. 1963;33:61-67. [CrossRef]
11. Tanyel FC, Erdem S, Altunay H, et al. Distribution and morphometry of fiber types in cremaster muscles of boys with inguinal hernia or undescended testis. *Pathol Res Pract*. 2000;196:613-617. [CrossRef]
12. Patapoutian A, Wold BJ, Wagner RA. Evidence for developmentally programmed transdifferentiation in mouse esophageal muscle. *Science*. 1995;270:1818-1821. [CrossRef]
13. Borirakchanyavat S, Baskin LS, Kogan BA, Cunha GR. Smooth and striated muscle development in the intrinsic urethral sphincter. *J Urol*. 1997;158:1119-1122. [CrossRef]
14. Perry RL, Rudnick MA. Molecular mechanisms regulating myogenic determination and differentiation. *Front Biosci*. 2000;5:D750-D767. [CrossRef]
15. Yuan FP, Li X, Lin J, et al. The role of RXFP2 in mediating androgen-induced inguinoscrotal testis descent in LH receptor knockout mice. *Reproduction*. 2010;139:759-769. [CrossRef]
16. Botti M, Ragionieri L, Cacchioli A, Gazza F, Panu R. Neurochemical features of the autonomic neurons projecting to the cremaster muscle of the boar. *Anat Rec (Hoboken)*. 2015;298:2091-2097. [CrossRef]
17. Youssef EH, Raslan NA. Study of the factors which affect the descent of the testicles in man. *Acta Anat (Basel)*. 1971;79:422-444. [CrossRef]
18. Tomiyama H, Sasaki Y, Huynh J, Yong E, Ting A, Hutson JM. Testicular descent, cryptorchidism and inguinal hernia: the Melbourne perspective. *J Pediatr Urol*. 2005;1:11-25. [CrossRef]
19. Yong WW, Sourial M, Farmer PJ, Southwell BR, Hutson JM. Does chemical sympathectomy alter the ontogeny of gubernacular migration in vivo? *J Pediatr Surg*. 2007;42:395-399. [CrossRef]
20. Sasaki Y, Hutson JM, Clarke MC. The role of sympathetic innervation in the developing rat gubernaculum. *J Pediatr Surg*. 2007;42:350-354. [CrossRef]
21. Tanyel FC, Ertunç M, Büyükpamukçu N, Onur R. Mechanisms involved in contractile differences among cremaster muscles according to localization of testis. *J Pediatr Surg*. 2001;36:1551-1560. [CrossRef]
22. Tanyel FC, Talim B, Kale G, Boyokpamukçu N. Differences in the morphology of the processus vaginalis with sex and underlying disease condition. *Pathol Res Pract*. 2000;196:767-770. [CrossRef]
23. Tanyel FC, Müftüoglu S, Dagdeviren A, Kaymaz FF, Büyükpamukçu N. Myofibroblasts defined by electron microscopy suggest the dedifferentiation of smooth muscle within the sac walls associated with congenital inguinal hernia. *BJU Int*. 2001;87:251-255. [CrossRef]
24. Mouravas VK, Koletsa T, Sfougaris DK, et al. Smooth muscle cell differentiation in the processus vaginalis of children with hernia or hydrocele. *Hernia*. 2010;14:187-191. [CrossRef]
25. Tanyel FC, Talim B, Kale G, Büyükpamukçu N. A reevaluation of the structures accepted to represent the postnatal gubernaculum. *Urol Int*. 2002;69:116-119. [CrossRef]
26. Sfoungaris D, Mouravas V, Koletsa T, Lambropoulos V, Kostopoulos I, Spyridakis I. Differences in the development of the processus vaginalis between children with undescended testis and inguinal hernia. *J Clin Neonat*. 2016;5:31-34. [CrossRef]
27. Piçarro C, Tatsuo ES, Amaral VF, Gomez RS, Cruzeiro PC, Lanna JC. Morphological comparison of processus vaginalis from boys with undescended testis and hernia sacs from boys with inguinal hernia. *Eur J Pediatr Surg*. 2009;19:145-147. [CrossRef]
28. Hosgor M, Karaca I, Ozer E, et al. The role of smooth muscle cell differentiation in the mechanism of obliteration of processus vaginalis. *J Pediatr Surg*. 2004;39:1018-1023. [CrossRef]
29. Öberg S, Andresen K, Rosenberg J. Etiology of Inguinal Hernias: A Comprehensive Review. *Front Surg*. 2017;4:52. [CrossRef]
30. Tanyel FC, Ulusu NN, Tezcan EF, Büyükpamukçu N. Total calcium content of sacs associated with inguinal hernia, hydrocele or undescended testis reflects differences dictated by programmed cell death. *Urol Int*. 2003;70:211-215. [CrossRef]
31. Tanyel FC, Sara Y, Ertunç M, Onur R, Büyükpamukçu N. Lack of carbachol response indicates the absence of cholinergic receptors in sacs associated with undescended testis. *J Pediatr Surg*. 1999;34:1339-1344. [CrossRef]
32. Waxham MN. Neurotransmitter receptors. In: Zigmund MJ, Bloom FE, Landis SC, Roberts JL, Squire LR, editors. Fundamental Neurosience. *San Diego: Academic Press* 1999:235-267. [CrossRef]
33. Bingöl-Koloğlu M, Tanyel FC, Akçören Z, et al. A comparative histopathologic and immunohistopathologic evaluation of cremaster muscles from boys with various inguinoscrotal pathologies. *Eur J Pediatr Surg*. 2001;11:110-115. [CrossRef]
34. Tanyel FC, Erdem S, Büyükpamukçu N, Tan E. Cremaster muscles obtained from boys with an undescended testis show significant neurological changes. *BJU Int*. 2000;85:116-119. [CrossRef]
35. Tanyel FC, Erdem S, Büyükpamukçu N, Tan E. Cremaster muscle is not sexually dimorphic, but that from boys with undescended testis reflects alterations related to autonomic innervation. *J Pediatr Surg*. 2001;36:877-880. [CrossRef]
36. Tanyel FC, Müftüoğlu S, Dağdeviren A, Karakoç L, Büyükpamukçu N. Ultrastructural deficiency in autonomic innervation in cremasteric muscle of boys with undescended testis. *J Pediatr Surg*. 2001;36:573-578. [CrossRef]
37. Tanyel FC, Okur HD. Autonomic nervous system appears to play a role in obliteration of processus vaginalis. *Hernia*. 2004;8:149-154. [CrossRef]
38. Molinaro F, Fusi G, Aglianò M, et al. Clinically Differentiated Abnormalities of the Architecture and Expression of Myosin Isoforms of the Human Cremaster Muscle in Cryptorchidism and Retractile Testis. *Urol Int*. 2020;104:891-901. [CrossRef]
39. Kim YS, Sainz RD. Beta-adrenergic agonists and hypertrophy of skeletal muscles. *Life Sci*. 1992;50:397-407. [CrossRef]
40. Chin H, Almon RR. Fiber-type effects of castration on the cholinergic receptor population in skeletal muscle. *J Pharmacol Exp Ther*. 1980;212:553-539. [CrossRef]
41. Vigneron P, Dainat J, Bacou F. Propriétés des fibres musculaires squelettiques. II. Influences hormonales [Properties of skeletal muscle fibers. II. Hormonal influences]. *Reprod Nutr Dev (1980)*. 1989;29:27-53. [CrossRef]
42. Keast JR. The autonomic nerve supply of male sex organs--an important target of circulating androgens. *Behav Brain Res*. 1999;105:81-92. [CrossRef]
43. Tanyel FC, Yüzbaşioğlu A, Kocaefe C, Orhan D, Ozgüç M. Androgen receptor immunostaining and androgen receptor messenger ribonucleic acid expression are increased in cremaster muscles associated with undescended testis. *Urology*. [CrossRef]
44. Bingöl-Koloğlu M, Demirci M, Büyükpamukçu N, Tanyel FC. Cremasteric reflexes of boys with descended, retractile, or undescended testes: an electrophysiological evaluation. *J Pediatr Surg*. 1999;34:430-434. [CrossRef]

45. Cherruau M, Facchinetti P, Baroukh B, Saffar JL. Chemical sympathectomy impairs bone resorption in rats: a role for the sympathetic system on bone metabolism. *Bone*. 1999;25:545-551. [CrossRef]
46. Bingöl-Koloğlu M, Sara Y, Tanyel FC, Onur R, Büyükpamukçu N, Hiçsönmez A. Contractility and electrophysiological parameters of cremaster muscles of boys with a hernia or undescended testis. *J Pediatr Surg*. 1998;33:1490-1494. [CrossRef]
47. Tanyel FC, Ulusu NN, Tezcan EF, Büyükpamukçu N. Less calcium in cremaster muscles of boys with undescended testis supports a deficiency in sympathetic innervation. *Urol Int*. 2002;69:111-115. [CrossRef]
48. Cooper, G.M. Cell signaling. In: Cooper GM, editor. The Cell: Molecular Approach. *Washington DC: ASM Press*. 1997:521-560. [CrossRef]
49. Schmid A, Renaud JF, Lazdunski M. Short term and long term effects of beta-adrenergic effectors and cyclic AMP on nitrendipine-sensitive voltage-dependent Ca2+ channels of skeletal muscle. *J Biol Chem*. 1985;260:13041-13046. [CrossRef]
50. Berchtold MW, Brinkmeier H, Müntener M. Calcium ion in skeletal muscle: its crucial role for muscle function, plasticity, and disease. *Physiol Rev*. 2000;80:1215-1265. [CrossRef]
51. Ulusu NN, Tandoğan B, Tanyel FC. Sarco(endo)plasmic reticulum and plasmalemmal Ca(2+)-ATPase activities in cremaster muscles and sacs differ according to the associated inguinal pathology. *Cell Biochem Funct*. 2007;25:515-519. [CrossRef]
52. Duman L, Demirci M, Tanyel FC. Heart rate variability analysis reveals a shift in autonomic balance towards an increase in parasympathetic tonus in boys with undescended testis. *Eur J Pediatr Surg*. 2010;20:150-152. [CrossRef]
53. Tanyel FC, Ertunç M, Ekinci S, Yildirim M, Onur R. Anti-androgen induced inhibition of testicular descent is associated with a decrease in sympathetic tonus. *Eur J Pediatr Surg*. 2005;15:273-278. [CrossRef]
54. Tanyel FC, Ertunç M, Ekinci S, Otçu S, Yildirim M, Onur R. Chemical sympathectomy by 6-OH dopamine during fetal life results in inguinal testis through altering cremasteric contractility in rats. *J Pediatr Surg*. 2003;38:1628-1632. [CrossRef]
55. Bingöl-Koloğlu M, Tanyel FC, Anlar B, Büyükpamukçu N. Cremasteric reflex and retraction of a testis. *J Pediatr Surg*. 2001;36:863-867. [CrossRef]
56. Iversen S, Iversen L, Saper CB. The autonomic nervous system and the hypothalamus. In: Kandel ER, Schwartz JH, Lessel TM, editors. Principals of Neural Science. *New York: McGraw-Hill*. 2000:960-981. [CrossRef]
57. Clapham DE. Signal transduction. Why testicles are cool. *Nature*. 1994 8;371:109-110. [CrossRef]
58. Eskola V, Paukku T, Warren DW, Huhtaniemi I. A novel role for testicular descent; temperature-dependent induction of pertussis toxin-sensitive Gi protein function in postnatal rat Leydig cells. *Endocrinology*. 1995;136:4659-4664. [CrossRef]
59. Reed JC. Mechanisms of apoptosis. *Am J Pathol*. 2000;157:1415-1430. [CrossRef]
60. Fuller GM, Shields D. The cell cycle and cell division. In: Fuller GM, Shields D, editors. Molecular basis of medical cell biology. *Appleton & Lange, Stamford*. 1998:106-123. [CrossRef]
61. Pan Z, Damron D, Nieminen AL, Bhat MB, Ma J. Depletion of intracellular Ca2+ by caffeine and ryanodine induces apoptosis of chinese hamster ovary cells transfected with ryanodine receptor. *J Biol Chem*. 2000;275:19978-19984. [CrossRef]
62. Szalai G, Krishnamurthy R, Hajnóczky G. Apoptosis driven by IP(3)-linked mitochondrial calcium signals. *EMBO J*. 1999;18:6349-6361. [CrossRef]
63. Kruman II, Mattson MP. Pivotal role of mitochondrial calcium uptake in neural cell apoptosis and necrosis. *J Neurochem*. 1999;72:529-540. [CrossRef]
64. Ma TS, Mann DL, Lee JH, Gallinghouse GJ. SR compartment calcium and cell apoptosis in SERCA overexpression. *Cell Calcium*. 1999;26:25-36. [CrossRef]
65. Beuermann C, Beck J, Schmelz U, et al. Tissue calcium content in piglets with inguinal or scrotal hernias or cryptorchidism, *J Comp Pathol*. 2009;140:182-186. [CrossRef]
66. De Miguel MP, Mariño JM, Gonzalez-Peramato P, Nistal M, Regadera J. Epididymal growth and differentiation are altered in human cryptorchidism. *J Androl*. 2001;22:212-25. [CrossRef]
67. Fan X, Robaire B. Orchidectomy induces a wave of apoptotic cell death in the epididymis. *Endocrinology*. 1998;139:2128-2136. [CrossRef]
68. Carvalho TL, Kempinas WG, Favaretto AL. Morphometric evaluation of the rat testis, epididymis and vas deferens following chemical sympathectomy with guanethidine. *Ann Anat*. 1993;175:453-457. [CrossRef]
69. Narcı A, Korkmaz M, Yakut T, Biltekin B, Bilir A, Tanyel FC. Smooth Muscle Cells are Derived Predominantly from Tissue Explant of Inguinal Hernia Sac. *J Curr Pediatr*. 2018:16:29-34. [CrossRef]
70. Chamley JH, Campbell GR. Trophic influences of sympathetic nerves and cyclic AMP on differentiation and proliferation of isolated smooth muscle cells in culture. *Cell Tissue Res*. 1975;161:497-510. [CrossRef]
71. Smith PG, Venkataraman P, Reddy H. Smooth muscle growth in the mature rat: role of sympathetic innervation. *J Auton Nerv Syst*. 1990;31:13-20. [CrossRef]
72. Tanyel FC, Ocal T, Karaağaoğlu E, Büyükpamukçu N. Individual and associated effects of length of inguinal canal and caliber of the sac on clinical outcome in children. *J Pediatr Surg*. 2000;35:1165-1169. [CrossRef]
73. Tanyel FC, Ocal T, Büyükpamukçu N. Excessive sac pressures: the pathogenesis and innocence of hydroceles in children. *BJU Int*. 2001;87:372-375. [CrossRef]
74. Job JC, Toublanc JE, Chaussain JL, Gendrel D, Garnier P, Roger M. Endocrine and immunological findings in cryptorchid infants. *Horm Res*. 1988;30:167-172. [CrossRef]
75. Rosa-e-Silva AA, Guimarães MA, Lamano-Carvalho TL, Kempinas WG. Chemical sympathectomy blocks androgen biosynthesis during prepuberty. *Braz J Med Biol Res*. 1995;28:1109-1112. [CrossRef]
76. Gendrel D, Roger M, Chaussain JL, Canlorbe P, Job JC. Correlation of pituitary and testicular responses to stimulation tests in cryptorchid children. *Acta Endocrinol (Copenh)*. 1977;86:641-650. [CrossRef]
77. Black IB, Bloom EM, Hamill RW. Central regulation of sympathetic neuron development. *Proc Natl Acad Sci U S A*. 1976;73:3575-3578. [CrossRef]
78. Orer HS, Zhong S, Barman SM, Gebber GL. Central catecholaminergic neurons are involved in expression of the 10-Hz rhythm in SND. *Am J Physiol*. 1996;270:R333-R341. [CrossRef]
79. Spergel DJ. Modulation of Gonadotropin-Releasing Hormone Neuron Activity and Secretion in Mice by Non-peptide Neurotransmitters, Gasotransmitters, and Gliotransmitters. *Front Endocrinol (Lausanne)*. 2019;10:329. [CrossRef]
80. Woolley MM. Cryptorchidism. In: Ravitch MM, Welch KJ, Benson CD, Eberdeen E, Randolph JG, editors. Pediatric Surgery. Chicago: Year Book Medical Publishers Inc. 1979;1399-1410. [CrossRef]