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SKILL AND TALENT

Bladder changes after several coverage modalities in the surgically induced model of myelomeningocele in lambs☆

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Abstract
Objective: To assess the presence of early bladder abnormalities in a prenatally corrected and uncorrected animal model of Myelomeningocele (MMC).
Method: A MMC-like lesion was surgically created in 18 fetal lambs between the 60th and the 80th day of gestation. Eight of them did not undergo fetal repair (group A), three were repaired with an open two-layer closure (group B), three using BioGlue® (group C) and four fetoscopically (group D). At term, bladders were examined macroscopically and histopathological changes were assessed using H–E and Masson Trichrome.
Results: Five animals in group A (5/8, 62%), two in group B (2/3, 66%), one in group C (1/3, 33%) and one in group D (1/4, 25%) survived. Macroscopically bladders in group A were severely dilated and showed thinner walls. Microscopically they showed a thin layer of colagenous tissue (Blue layer. BL) lying immediately subjacent to the urothelium. The muscular layers were thinner. Non compliant pattern with thick wall and low capacity was also found in the non corrected model. Group B and the control showed preservation of muscular layers and absence of BL. Groups C and D presented BL but also preservation of muscular layers.
Conclusion: Bladder changes in a surgically induced model of MMC can be described using histopathological data. Both extremes of bladder changes can be observed in the model. These changes were completely prevented with open fetal surgery and partially with other coverage modalities.

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PALABRAS CLAVE
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Capa azul

Cambios en la vejiga después de varias modalidades de cobertura en el modelo de mielomeningocele inducido quirúrgicamente en corderos

Resumen

Objetivo: Determinar las anomalías vesicales precoces en un modelo animal de mielomeningocele (MMC) con y sin corrección quirúrgica intraútero.

Método: Creamos una lesión similar al MMC en 18 fetos de cordero entre los días 60 y 80 de gestación. Ocho de ellos no se repararon prenatalmente (grupo A), 3 se intervinieron mediante cierre abierto en 2 planos (grupo B), 3 se cerraron con pegamento biológico (grupo c) y 4 por fetoscopia (grupo D). Al final de la gestación las vejigas se estudiaron macroscópica e histológicamente usando tinción de hematoxilina-eosina y tricrómico de Masson.

Resultados: Cinco animales del grupo A (5/8, 62%), 2 en el grupo B (2/3, 66%), uno en el grupo C (1/3, 33%) y uno en el grupo D (1/4, 25%) sobrevivieron. Macroscópicamente las vejigas del grupo A estaban muy dilatadas y sus paredes eran muy finas. Microscópicamente mostraban una delgada capa de colágeno (capa azul [CA]) inmediatamente por debajo del urotelio; las capas musculares estaban muy adelgazadas. En el grupo no corregido también encontramos vejigas de baja acomodación, con paredes engrosadas y capacidad disminuida. El grupo B y el control mostraban preservación de las capas musculares y ausencia de CA. Los grupos C y D presentaban CA y preservación de las capas musculares.

Conclusión: Los cambios vesicales en el modelo quirúrgico de MMC en corderos pueden describirse mediante datos histopatológicos. Ambos extremos del espectro pueden darse en dicho modelo. Estos cambios pueden prevenirse por completo mediante cirugía fetal abierta y parcialmente a través de otras formas de cobertura.

Introduction

Myelomeningocele (MMC) is a defect in the neural tube formation that represents the most frequent form of myelodisplasia with an incidence of 1/2000 live births. The lesion is characterized by the protrusion of meninges and medulla through the vertebral defect, leading to multiple disabilities at different levels: paraplegia, bladder and intestinal dysfunction, and Arnold-Chiari malformation.

Therefore, MMC is the most common cause of neurogenic bladder dysfunction in children (NBD). As it is known, NBD is accompanied by a number of well-described clinical and physiopathological patterns: loss of voluntary micturition control, detrusor overactivity, bladder/sphincter dyssynergia, increased bladder pressure, and hypertrophy. The range of bladder changes ranges from an atonic poorly emptying bladder with miogenic failure to a non-compliant bladder, resulting in urinary incontinence and making necessary multiple surgical procedures, clean intermittent catheterization (CIC), and a close follow-up to achieve continence and avoid renal function deterioration.

It is postulated that MMC causes damage to the neural placode for two reasons (two-hit hypothesis): the original neural tube defect and the further exposure to the intrauterine environment and trauma.[1] Several clinical and experimental studies have suggested that fetal surgical intervention to repair the defect could ameliorate this secondary lesion.[2] Like the group of Philadelphia, which used a model of retinoic acid (RA)-induced MMC in fetal rats to assess functional and structural characteristics of the detrusor muscle in this NBD model. The resulting pathology has morphological and clinical similarities with human MMC, since the original neural tube defect and the posterior exposure are both present. They conclude that peripheral neural supply deteriorates throughout gestation and that, despite normal structural development, the functional status of the detrusor smooth muscle has already been altered in this model.[3]

On the other hand, the California group reported in 2006 an experimental work with adult female rats that underwent bilateral L5–S2 ventral root avulsion injury, followed, in some of them, by an acute implantation of the avulsed L6 and S1 roots into the conus medullaris. They concluded that implantation of avulsed roots promotes reinnervation of the urinary tract and return of micturition reflexes.[4]

Clinical studies of urodynamic outcome in patients with prenatally treated MMC have been reported by different groups and all of them agreed that the results were similar to those with conventional postnatal treatment.[1,5–7]

Histopathological bladder studies that could only be achieved with an experimental animal model could add some information to this clinical data. So, even though it is not a new concept and several groups had worked with different models, it remains a challenge.

The surgically induced model of MMC in sheep has strong resemblances with the human disease and the prevention of urinary incontinence after open fetal surgery has been described in this model; nevertheless, no histopathological bladder description has been reported previously.[8,9] Our goal was to examine if this surgically induced model of MMC in sheep produces bladder changes similar to those found in human MMC. Finally, potential prevention of these changes using different prenatal treatments was also tested.