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MRI ANATOMY OF LYSYL OXIDASE LIKE-1 DEFICIENT (LOXL1 KO) MICE WITH AND WITHOUT PELVIC ORGAN PROLAPSE (POP): A PILOT STUDY

Hypothesis / aims of study : Female pelvic floor dysfunction (FPFD) is a complex and often debilitating group of conditions which include urinary incontinence, voiding dysfunction, pelvic organ prolapse, and anal incontinence. These disorders affect up to 75% of women, and require surgery in 11% of women, yet, little is known about their pathophysiology. In 2004, Liu et al. noted that mice lacking the protein, lysyl oxidase-like 1 (LOXL1) routinely develop pelvic organ prolapse [1]. LOXL1 is a copper-dependent monoamine oxidase required to synthesize elastin polymers from tropoelastin monomers in adult tissues. LOXL1 knockout (LOXL1 KO) mice develop pelvic organ prolapse after pregnancy and delivery or with aging, presumably due to an inability to maintain homeostasis of mature elastic fibers. In 2006, Liu et al, further characterized the FPFD seen in these mice [2]. LOXL1 KO mice develop overt prolapse 1-3 days post partum (Acute Stage), which retracts over 1-2 weeks, leaving a persistent perineal bulge with internal pelvic organ descent (Stable Stage). The vaginal wall was noted to be markedly distended with uterine descent into the upper vagina. These observations were made after animals were sacrificed. It is unclear whether these changes are present and as pronounced in vivo. Furthermore, in humans, clinical examination has shown poor correlation with radiologic studies [3]. Lastly, because sacrifice is required to view the internal anatomy, longitudinal studies of changes in internal pelvic anatomy over time can not be performed. To date, no technique has been used to understand changes in internal pelvic anatomy in vivo in LOXL1 KO mice. If a feasible and accurate technique can be described, longitudal studies can be performed using this animal model of FPFD. The objective of the study was to determine the feasibility of small animal MRI imaging to describe differences in female pelvic anatomy between LOXL1 KO mice with and without POP.

Study design, materials and methods: Female LOXL1 KO mice with and without POP were used in the experiment. Prolapsed mice were parous and had stage III POP, and non-prolapsed mice were nulliparous and had stage 0 POP by the MOPQ staging system. Animals were anesthetized with isoflurane inhalation anesthetic and placed in a 7 Tesla Bruker Biospec MRI scanner. High resolution (600um x 200um x 200um) T1-weighted, fat-suppressed images were obtained with a turbo-spin echo sequence (TR/TE = 1500ms,20ms, 4 echoes) to visualize the pelvic anatomy in detail. Images were viewed serially using Volsuite 3.3.20 image processing software. Mice were sacrificed after imaging. Gross anatomic dissections were performed, and digital images of the female pelvic structures were obtained.

Results: Age-matched mice with POP (n=2) and without POP (n=2) were studied. Qualitative analysis revealed increased variability in the size and location of the bladder in prolapsed mice compared with non-prolapsed mice, with the bladder below the pubic symphysis and distending the perineum in one mouse. The maximum bladder diameter was measured to be 14 mm, with noticeable bladder wall thickening of 0.4mm. In the second prolapsed mouse the bladder was located normally, however the vagina was markedly distended, leading to perineal distension. The rectum could be seen protruding outside the body in both prolapsed animals. The mice without POP demonstrated a uniform bladder size and location. In the mice without POP, the vagina, uterus, cervix, and rectum were observed in consistent anatomic positions.(Figure 1)

Interpretation of results: MRI is a technically feasible investigational tool which is able to identify important anatomic differences between LOXL1 KO mice with and without POP. LOXL1 mice have variable internal pelvic anatomy, and clinical examination may not accurately describe internal pelvic anatomy in prolapsed LOXL1 KO mice.

Concluding message: Small animal MRI is a promising technique for studying anatomic changes in mice with FPFD. Its advantages over current anatomic study techniques are that studies can be performed in vivo and longitudinally. Future studies with larger numbers of animals and quantitative image processing techniques are warranted.

Figure 1: MRI Images of Prolapsed and Non-Prolapsed LOXL1 KO Mice

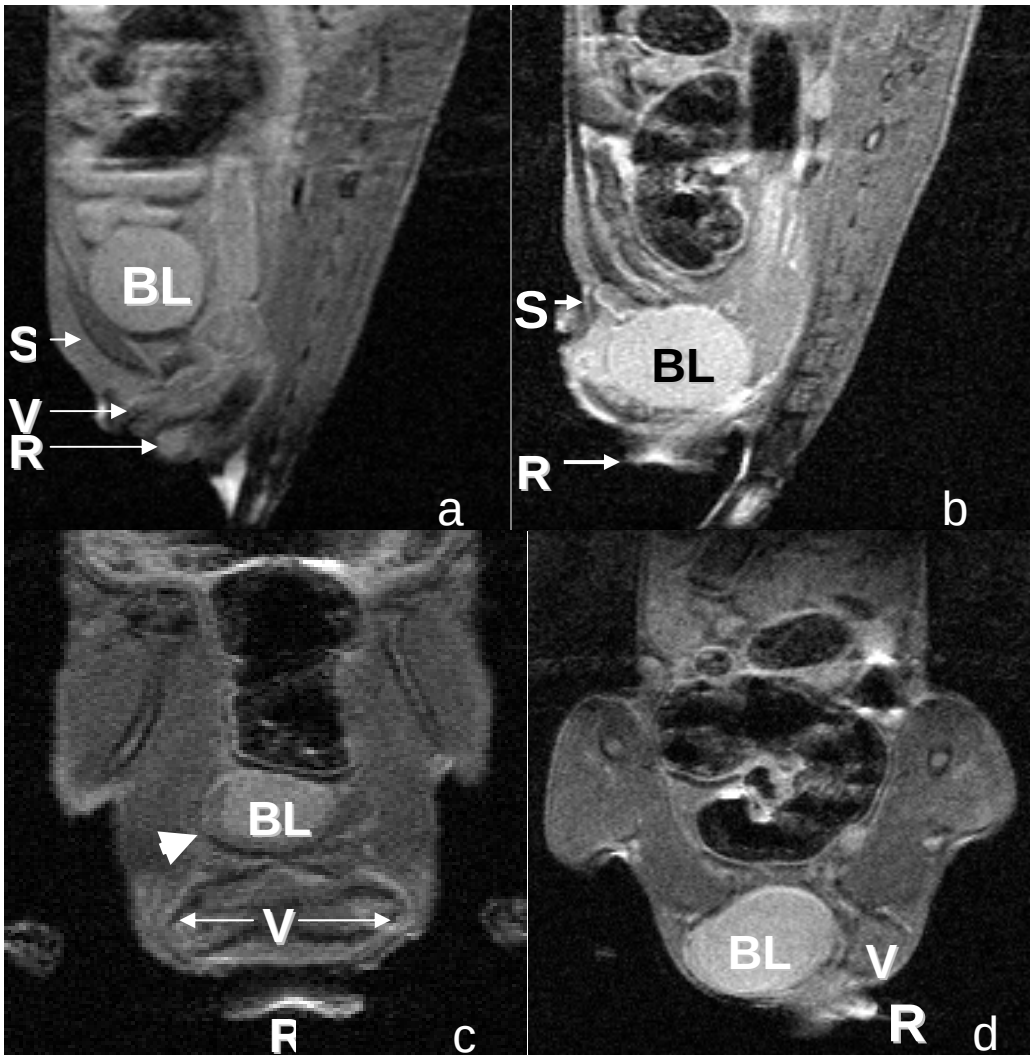

Figure 1 –a) Sagittal view of a non-prolapsed LOXL 1 KO mouse. Note the narrow vagina, bladder above the pubic symphysis and rectum within the perineum. b) Sagittal view of a prolapsed LOXL1 KO mouse. Note the bladder below the pubic symphysis, and rectum outside of the perineum. The vagina is not visible in this view. c) Coronal view of a prolapsed LOXL1 KO mouse. Note the markedly distended vagina and the thickened bladder wall (thick arrow).d) the same prolapsed LOXL1 KO mouse as in panel b. Note the bladder fills the perineal bulge and displaces the vagina. S=pubic symphysis, BL=bladder, V=vagina, R=rectum.

References:

1. Nature Genetics. 2004 Feb;36(2):178-82.
2. American Journal of Pathology. 2006 Feb;168(2):519-28.
3. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8(6):336-9.

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ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by Case Western Reserve University Institutional Animal Care and Use Committee