1. INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of disorders characterized by inherited abnormalities of connective tissue. The main clinical manifestations of this disease are skin fragility, skin hyperextensibility and joint hypermobility. More than 10 subtypes of EDS have been defined based on clinical, genetic and biochemical criteria. Recent molecular studies of EDS have identified genetic defects responsible for several subtypes of this disease; however, for others, the molecular defect remains unknown.

Clinical pathologies associated with EDS may include the presence of diverticuli in different organs. Diverticuli of the gastro-intestinal tract, as well as the genito-urinary tract have been reported. Non-EDS diverticuli of the urinary bladder have frequently been associated with urinary tract infections, dysuria, hematuria, and vesicoureteral reflux. As a result, diverticulectomy has often been advocated as the treatment of choice. The durability of this treatment plan is often questioned, since the EDS-associated bladder diverticuli form a distinct group characterized by postoperative recurrence. Levard et al. have speculated that the recurrence of these diverticuli supports the theory that there is an intrinsic anomaly of the vesical wall in certain subtypes of EDS.

In this study, we report the results of a detailed investigation of the native bladder wall and bladder diverticular wall of a child who has been diagnosed clinically with EDS. Native bladder wall and congenital diverticular wall of a child who did not present with EDS were used for comparison.
2. MATERIALS AND METHODS

2.1. Patients

A twelve year old girl with a prior clinical diagnosis of Ehlers Danlos syndrome presented to the Urology Clinic with a history of new onset urinary incontinence and urinary frequency. She initially presented to our institution at birth with skeletal abnormalities, bilateral hip and knee dislocations, joint hypermobility and lax eyelids. Investigation at that time led to the diagnosis of EDS (type VII). Neither parent reported symptoms of EDS.

More recently the patient reported a voiding history characterized by urinary frequency of one hour intervals, and day and nighttime urinary incontinence. Her voiding was characterized by straining and the need to apply manual compression to the suprapubic region to empty her bladder. She reported occasional suprapubic pain. Urine analysis was normal and urine culture was with no growth of microorganisms. Urological imaging consisted of a renal ultrasonograph with two normal kidneys, and a voiding cystourethrogram (VCUG) with a greater than 700ml capacity, trabeculation, and a large left-sided diverticulum which did not empty with voiding. Urodynamic studies demonstrated a bladder capacity of 1150ml, a residual of 775ml, and a voiding pattern consistent with abdominal valsalva maneuvers.

Treatment options of clean intermittent catheterization and diverticulectomy were discussed with the patient and family, with diverticulectomy chosen. Postoperatively the patient has done well, voiding to completion with resolution of urinary frequency and incontinence. Postoperative urodynamic studies revealed a bladder capacity of 350ml, a residual of 75ml, and a voiding pattern characterized by a coordinated and sustained detrusor contraction.

A four and a half year old boy with no prior medical history, presented to the Urology Clinic with a febrile urinary tract infection and a left pyelonephritis. The patient’s urological history was only significant for decreased force of his urinary stream. His evaluation included a renal ultrasonograph which was normal, and a VCUG which showed left vesicoureteral reflux and a left paraureteral diverticulum. The VCUG also demonstrated a dysfunctional voiding pattern with the diverticulum enlarging with voiding and a large post void residual urine. His treatment plan consisted of a bladder diverticulectomy and left ureteral reimplantation. Postoperatively the patient has done well with an improved urinary stream and no further febrile urinary tract infections.

Tissue from both the diverticulum and native bladder wall (non-diverticulum) were removed from both patients at the time of diverticulectomy. Pieces of tissue were then further divided for histologic, immunofluorescent, biochemical, molecular and physiologic analyses, as described below.

2.2. Histology and Immunofluorescence Histochemistry

All tissues were embedded in freezing compound (OTC) and 5 micrometer thick frozen sections were cut on a Slee cryostat (London, U.K.) maintained at -28°C. All specimens were stained utilizing Masson’s trichrome technique for routine histologic examination. For immunohistochemistry, sections were incubated with collagen type-specific antibodies, elastin and fibrillin-1 antibodies as previously published. Slides were examined with a Zeiss microscope equipped with epifluorescence optics and also, with a confocal laser scanning immunofluorescent microscope.

The human type III collagen monoclonal antibody was prepared and characterized in our laboratory and used undiluted. The type IV and type I collagen monoclonal antibod-