

EXT2 -related nephropathy with severe podocyte injury and modifiable proteinuria

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Abstract

Autosomal-recessive *EXT2*-related disease is a rare multisystem disorder with poorly characterized kidney involvement. We describe a 2-year-old girl homozygous for the founder complex allele *EXT2*:c.[260T > G;283C > T], p.[Met87Arg;Arg95Cys], who developed severe albumin-predominant proteinuria with preserved kidney function. Kidney biopsy showed diffuse podocyte foot-process effacement (> 80%) with minimal chronic injury, focal glomerular basement membrane irregularity, and mild mesangial remodeling. Daily prednisone reduced the urine protein-to-creatinine ratio from 903 to 342 mg/mmol and increased serum albumin from 32 to 36 g/L, but the response was not sustained after tapering. Following corticosteroid withdrawal, enalapril reduced the urine protein-to-creatinine ratio from 666 to 385 mg/mmol while serum albumin remained 36 g/L. Impaired heparan-sulfate assembly may therefore contribute to severe podocyte injury while leaving the downstream proteinuric phenotype modifiable. The responses to corticosteroids and enalapril support sequential, quantitatively monitored treatment rather than assuming that monogenic disease is therapeutically irreversible.

Summary - What is new

Severe podocyte injury with little chronic damage is a previously unrecognized phenotype of biallelic *EXT2* disease, and its downstream proteinuria remains therapeutically modifiable.

Case presentation

A 2-year-old girl from an Old Order Mennonite founder population was referred with syndromic neurodevelopmental disease and persistent proteinuria. Genetic testing demonstrated homozygosity for the *EXT2* complex allele c.[260T>G;283C>T], p.[Met87Arg;Arg95Cys], previously associated with seizures-scoliosis-macrocephaly syndrome. Earlier affected relatives had been reported to have hematuria, proteinuria, hypertension and kidney failure[1]. To our knowledge, no prior kidney biopsy findings have been reported in biallelic *EXT2* disease.

Follow-up information obtained from the parents of the four originally reported affected individuals, with written consent, indicated that one died from epilepsy at 16 years of age and the other three died from kidney failure during adolescence or young adulthood. Although detailed longitudinal kidney measurements and histopathology were unavailable, these outcomes suggest that the renal phenotype associated with this founder allele may be progressive and severe.

The patient's urine protein-to-creatinine ratio (UPCR) was repeatedly 800-900 mg/mmol and urine albumin-to-creatinine ratio approximately 900 mg/mmol. Serum albumin was 32-33 g/L. Cystatin C was 0.87 mg/L, with estimated GFR approximately 104-113 mL/min/1.73 m². There was no sustained hypertension, and kidney ultrasonography showed no structural explanation for the proteinuria.

Kidney biopsy showed a predominant podocytopathy. Electron microscopy demonstrated diffuse foot-process effacement involving more than 80% of the glomerular capillary surface. Most glomerular

basement membranes (GBMs) were preserved and mean thickness (approximately 200-290 nm) was appropriate for age, although occasional loops showed inner-zone clearing with subtle lamellation or splitting. There was mild segmental mesangial matrix expansion, very focal mesangial interposition and focal double-contour formation. Sparse electron-dense deposits were predominantly mesangial or paramesangial, with rare subendothelial and subepithelial deposits. Immunofluorescence showed mild segmental IgA and C3 staining; IgG and C1q were negative. Type IV collagen $\alpha 2/\alpha 5$ staining was normally distributed, including preserved linear $\alpha 5$ staining of GBM, Bowman capsule and tubular basement membranes. There was little chronic tubulointerstitial injury (Fig. 1a-c).

Prednisone 60 mg/m² daily was administered for 6 weeks, followed by alternate-day treatment for 4 weeks. During daily treatment, UPCR fell to approximately 300 mg/mmol and serum albumin increased to 36 g/L. Proteinuria subsequently returned to approximately 600-700 mg/mmol during alternate-day therapy and after withdrawal. The response was substantial, dose-dependent and incomplete, arguing for a direct antiproteinuric effect rather than a durable immunological remission (Fig. 1d). The magnitude of the changes exceeded the variability observed during repeated pretreatment measurements. Following corticosteroid withdrawal, enalapril was initiated at 0.1 mg/kg twice daily. At age 2.89 years, UPCR had decreased from 666 to 385 mg/mmol and UACR was 351.1 mg/mmol, while serum albumin remained 36 g/L. There was no hypotension, hyperkalemia, or deterioration in kidney function. This response to renin–angiotensin system blockade provided additional evidence that the downstream proteinuric phenotype remained modifiable.

Interpretation

EXT1 and EXT2 form the Golgi glycosyltransferase complex that elongates heparan-sulfate (HS) chains [2]. In fibroblasts from individuals carrying this complex allele, mutant EXT2 protein was markedly reduced but detectable, while NDST1 protein—required for HS N-sulfation—was absent despite preserved transcript [1]. The allele is therefore likely hypomorphic, potentially producing HS chains that are reduced in abundance or length and qualitatively abnormal in sulfation; these properties have not been measured directly.

HS proteoglycans are not simply a charge barrier. Agrin, perlecan and cell-surface proteoglycans organize basement membrane, bind signaling ligands and participate in integrin- and dystroglycan-mediated podocyte adhesion [3-5]. Experimental interruption of podocyte HS assembly can produce foot-process effacement and focal GBM abnormalities without necessarily causing marked proteinuria or generalized GBM thickening [4]. We therefore speculate that altered HS structure in EXT2 deficiency destabilizes the podocyte cytoskeleton and contributes to foot-process effacement. Although focal GBM abnormalities were present, the dominant lesion was extensive podocyte injury, suggesting that disruption of the cellular filtration barrier may be more important than structural matrix abnormalities in generating proteinuria. The partial steroid response supports the view that podocyte function remains at least partly modifiable despite the underlying genetic defect.

The focal IgA/C3 staining and sparse deposits were insufficient to diagnose a second immune-complex glomerulonephritis. Likewise, focal lamellation was morphologically Alport-like but, with normal collagen IV distribution and age-appropriate mean GBM thickness, did not support a collagen IV nephropathy. These observations illustrate why genetic diagnosis should not terminate routine renal phenotyping, including complete ultrastructural assessment.

Derivation of treatment

The therapeutic goal is not correction of EXT2, but modification of its downstream glomerular consequences. Reproducibly elevated pretreatment proteinuria and its reduction from 903 to 342 mg/mmol during daily prednisone provided clinical evidence that the downstream glomerular phenotype was at least partly modifiable despite an underlying monogenic disorder. Because the antiproteinuric effect was not sustained during alternate-day treatment and after withdrawal, prolonged high-dose corticosteroid therapy was not pursued. Instead, management was structured as a sequential, prespecified therapeutic experiment.

Renin–angiotensin system blockade was subsequently introduced to reduce glomerular capillary-wall stress. Enalapril 0.1 mg/kg twice daily reduced UPCR from 666 to 385 mg/mmol, with preservation of serum albumin and kidney function. Enalapril will be titrated according to blood pressure, potassium, kidney function, and antiproteinuric response. Additional interventions will be considered only if substantial proteinuria persists despite maximally tolerated supportive therapy.

A monogenic diagnosis predicts the initiating mechanism, not the reversibility of every downstream lesion. In ultra-rare diseases with an unfavorable but poorly characterized natural history, careful pathology and quantitative N-of-1 therapeutic trials may identify a window in which progression is not yet inevitable.

Declarations

Ethics approval: In accordance with Western University institutional policy, research ethics board approval was not required for this clinical report. Written consent was obtained for publication of the principal case and for inclusion of follow-up outcome information concerning the previously reported affected kindred.

Consent to participate: Not applicable.

Consent for publication: Written informed consent was obtained from the child's parent(s)/legal guardian(s) for publication of the clinical information and de-identified clinical, laboratory, genetic, and renal biopsy findings.

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Data availability: Data sharing is not applicable because this clinical report contains potentially identifiable information concerning an ultra-rare disorder.

Author contributions: GF conceived the report, directed clinical care and drafted the manuscript. MG reported the kidney biopsy and selected pathological images. AH also interpreted the kidney biopsy and reviewed the pathological images. VS interpreted the genetic diagnosis and revised the manuscript. All authors approved the final manuscript.

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Figures

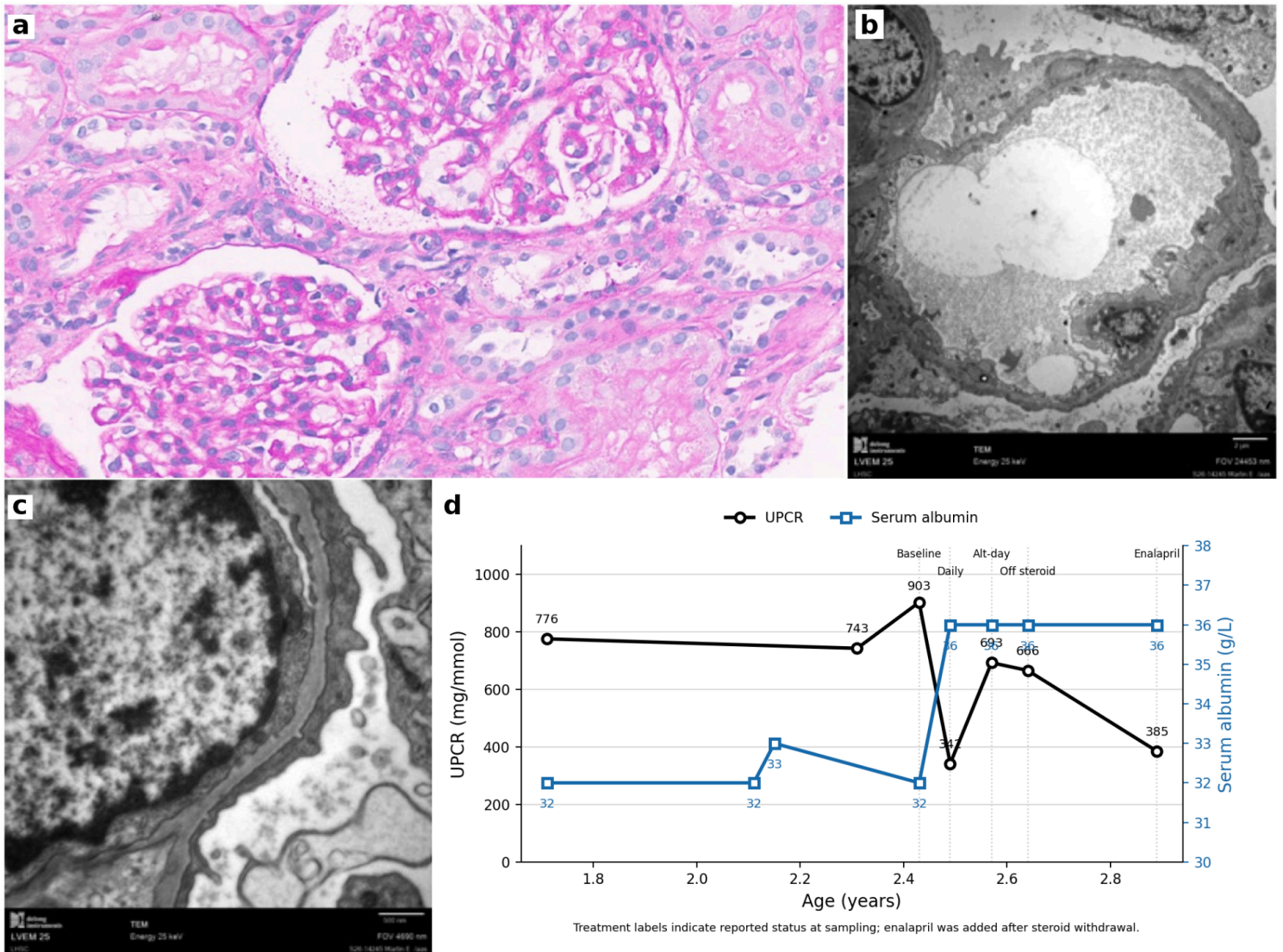


Figure 1

Histopathological findings and therapeutic implications in *EXT2*-related nephropathy.

- (a) Masson trichrome stain demonstrating preserved glomerular architecture with minimal chronic tubulointerstitial injury despite severe proteinuria.
- (b) Electron micrograph showing diffuse podocyte foot-process effacement involving more than 80% of the glomerular capillary surface, consistent with severe podocyte injury.
- (c) Higher-magnification electron micrograph demonstrating focal inner glomerular basement membrane clearing with subtle lamellation/splitting.
- (d) Longitudinal changes in UPCR and serum albumin during daily prednisone treatment, alternate-day treatment, corticosteroid withdrawal, and subsequent enalapril therapy. Proteinuria decreased during daily prednisone, rebounded after corticosteroid tapering, and decreased again after enalapril initiation, supporting biological modifiability of the downstream glomerular phenotype.