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Kidney disease is one of the main target organ features of Fabry Disease, and our understanding of the pathogenesis has evolved over time. 20 years ago, we thought that the main issue was glycolipid accumulation in endothelial cells. So as endothelial cells ballooned and the lumen inside the vessels got narrower and narrower, giving rise to ischemic kidney injury.

We now know this is not the case. So in recent years, there have been publications on kidney biopsies from children with Fabry Disease, and we now know that the main site of glycolipid accumulation in the kidney in Fabry children is the podocyte.

Retrospectively, this is quite easy to understand. Podocytes are terminally differentiated cells that do not divide. So as they do not divide, they will never divide the amount of glycolipids between daughter cells. They accumulate glycolipids over the years and years, over the decades. Huge accumulation of glycolipids in podocytes And this gives rise to podocyte injury, and this originates pathological albuminuria.

Pathological albuminuria will develop in childhood, when-- let's just speak about Fabry males, which are the ones who have the full-blown disease always. Classic Fabry males will develop pathological albuminuria at age eight, 10, 12, 15. And this pathological albuminuria will slide, slowly rise, to overt proteinuria levels, very similar to the pathogenesis and natural history of diabetic nephropathy-- early albuminuria, progressing to overt proteinuria, and eventually giving rise to a slowly progressive loss of glomerular filtration rate, until patients need dialysis at a mean age of around 40 years, both in males and in the few females-- and in the few females who eventually need renal replacement therapy.

So knowing this, how can we that knows early on kidney disease in Fabry patients? Well, in childhood, we should assess for urinary albumin-creatinine ratio. So we should be looking for microalbuminuria, for pathological albuminuria, but always doing this ratio from urinary albumin to urinary creatinine. Why? Because another early feature of Fabry Disease is polyurea, an inability to fully concentrate urine. This is a result of tubular involvement in the Henle's loop and distal nephrons.

And as a result of this polyuria, which patients may not manifest because normal urinary volume is so variable, so dependent on the amount of water we drink, that patients may not be aware. But if they are polyuric, if they do not concentrate urine, the urinary strip assessment of proteinuria may be negative.

Because of the high volume of urine, the proteins will be diluted. So early assessment of kidney involvement in Fabry Disease in children, you will need to assess urinary albumin-creatinine ratio. Later on, I'll put-- maybe I will increase to the overt proteinuria range. So the urinary protein-creatinine ratio will become pathological.

When are we talking about pathological proteinuria? Probably in their 20s, 20s or early 30s. And from age 30 on, glomerular filtration rates will progressively increase at quite a fast rate. So once patients are losing glomerular filtration rate, they will use it at around 5 to 10 ml per min per year, pretty similar to the rate of glomerular filtration rate in diabetic nephropathy.

So in summary, Fabry Disease at the kidney level is mainly a podocyte disease. This will result in pathological albuminuria in childhood, in overt proteinuria in the early adulthood, and in loss of renal function and in dialysis at around age 40, both in males-- classic males-- and in a few percentage of females. Around 5% to 10% of females will have this severe kidney disease. Most other females will not have severe kidney disease, and they will never need dialysis.