ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2021;92(2):263-267
DOI: 10.32641/andespediatr.v92i2.3013

CLINICAL CASE

# A secondary focal segmental glomerulosclerosis due to prematurity

## Glomeruloesclerosis focal y segmentaria secundaria a la oligonefronia del prematuro

**Gloria Valdés[a], Colomba Norero[b], Gonzalo P. Méndez[c]**

[a]Departamento de Nefrología, Facultad de Medicina, Pontificia Universidad Católica de Chile. Santiago, Chile.
[b]Facultad de Medicina Universidad de Chile. Santiago, Chile.
[c]Departamento de Anatomía Patológica, Facultad de Medicina, Pontificia Universidad Católica de Chile. Santiago, Chile.

Received: August 11, 2020; Approved: September 3, 2020

**What do we know about the subject matter of this study?**

Over the past 30 years, evidence has accumulated regarding the increased risk of kidney injury in preterm and low-birth-weight newborns secondary to incomplete glomerular development, which leads to glomerular hyperfiltration and focal and secondary sclerosis.

**What does this study contribute to what is already known?**

It presents the course of a premature, low-birth-weight newborn whom at 13 years of age presented focal segmental glomerulosclerosis which evolved to end-stage renal failure 26 years later, intending to emphasize the importance of early detection and management of susceptible subjects.

## Abstract

Both premature birth and low birth weight compromise nephron development. The lower nephron endowment is subjected to compensatory hyperfiltration that overloads the glomeruli and leads to the vicious circle of progressive deterioration of renal function. **Objective:** To emphasize the risk of renal involvement in this susceptible population by describing the case of a patient with long-term follow-up. **Clinical Case:** Low-weight premature newborn, who presented at 3 years of age severe hypertension, which was controlled with different types of antihypertensive drugs. However, 10 years later subnephrotic proteinuria was detected; a renal biopsy confirmed a focal and segmental glomerulosclerosis. Despite blocking the renin-angiotensin system for 23 years, his renal function progressively deteriorated, until requiring chronic hemodialysis during the last 3 years. **Conclusion:** It is essential to increase the awareness of the risk of renal damage in premature and low weight newborns in order to establish management that covers from gestation to adult life and to achieve an individual and epidemiological impact on renal health.

**Keywords:**
Preterm Birth;
Low Birth Weight;
Kidney Development;
Oligonephronia;
Focal Segmental Glomerulosclerosis;
Renal Failure

Correspondence:
Gloria Valdés
gvaldesst@gmail.com

How to cite this article: Andes pediatr. 2021;92(2):263-267. DOI: 10.32641/andespediatr.v92i2.3013

## Introduction

The kidney of preterm infants poses a great challenge to neonatologists, general pediatricians, and nephrologists as demonstrated by a recent review that proposes a pathophysiological approach to guide clinical management[1]. Since the most characteristic kidney injury associated with prematurity and low-birth-weight (LBW) is focal segmental glomerulosclerosis (FSGS)[2], we present the case of a preterm child born in 1981 and followed up to date, which describes how altered programming of nephron number and subsequent adaptive mechanisms typically affect morphology and lead to chronic/end-stage kidney disease.

The evolution of the anatomical and functional deterioration could likely have changed if the patient had been managed from birth onwards, according to the consequences of nephron reduction observed by Brenner in 1988 and 1994[3,4]. Preventing the defect in the programming of nephrons (a disease that originated from an inadequate intrauterine development) also requires the incorporation of new ways of managing obstetric pathologies that contribute to trigger preterm labor[5,6,7]. The objective of this clinical case report is to emphasize the risk of renal involvement in this susceptible population by describing the case of a patient with prolonged follow-up.

## Clinical Case

A 39-year-old male, born in 1981, the fourth child of a 38-year-old mother, who had normal blood pressure during gestation and has not developed hypertension up to date. However, since the third gestational month she presented uterine contractions. At 20 weeks of gestation, intrauterine growth restriction was detected and at 30 weeks a C-section was performed due to chronic fetal distress and oligohydramnios. The newborn weighed 1,800 g.

At 3 years of age, he was referred to the Pediatric Nephrology Outpatient Clinic of the *Hospital San Juan de Dios* with the diagnoses of weight and height deficiency (10$^{th}$ percentile) and severe essential hypertension. During the following 10 years, he maintained weight and height in the 10$^{th}$ percentile. He sequentially received several antihypertensives, as beta-blockers, calcium channel blockers or diuretics, presenting blood pressures within the normal range for age, normal renal function, and renal ultrasound growth consistent with his height.

At 13 years of age, the detection of a non-nephrotic proteinuria lead to a percutaneous kidney biopsy. The light microscopy examination showed renal cortical tissue with 21 hypertrophic glomeruli and prominent juxtaglomerular apparatus (figure 1 A and B). Five of them showed segmental sclerosing lesions with hyaline features and focal synechiae (figure 1, A and B). The tubulointerstitial and vascular compartments also showed signs of chronic damage, particularly severe in the later (figure 1 A).

The histomorphometric analysis showed a glomerular density of 0.65/mm$^2$ (N (Normal) = 7), an average diameter of 393 μU and an area of 0.121 mm$^2$ (N = 0.015 mm$^2$); in the cell number in the glomeruli without segmental lesion was 160 (N = 83) and that of the juxtaglomerular apparatus 25 (N = 1.1-1.5); all normal values[8-11] (figure 1 B).

The immunofluorescence was mildly positive for IgM in the mesangium with comma-shaped pattern, and in arterioles was positive for C3. Electron microscopy showed a slightly increased mesangial matrix with some type I collagen fibers and poorly defined densities (figure 1 C and D). The main finding was a focal prominent podocyte foot process effacement.

After establishing the diagnosis of oligomeganephronia and secondary focal segmental glomerulosclerosis, enalapril was started; this was later changed to long-acting renin-angiotensin system (RAS) blockers. His renal function slowly deteriorated and at 36 years of age he was admitted to chronic hemodialysis.

## Discussion

In this case the subnephrotic proteinuria and the renal biopsy correspond to the FSGS described in preterm patients with very low birth weight for gestational age[2]. This secondary form of FSGS is a consequence of hemodynamic adaptations due to the low number of functioning nephrons that leads to increased intracapillary pressure causing hyperfiltration, microaneurysms, ruptures, podocyte detachment, and sclerosis of capillary loops due to the accumulation of hyaline material that can lead to its occlusion.

In the fine ultrastructural analysis, the cytoplasmic and mainly the alterations in the pedicellar processes of the podocytes can be focally intense, but always patchy and variable from one glomerulus to the other. This particular morphological characteristic allows the differential diagnosis with the diffuse or primary form of podocyte injury. The clinical characteristics correlate in most of these cases with non-nephrotic proteinuria, absence of edema or hypoalbuminemia, which can progress to the nephrotic range, according to the evolution of the secondary glomerular destruction[12].

The early onset of hypertension in the case we describe was probably the result of persistent fetal hypoperfusion that stimulated the juxtaglomerular apparatus, which caused severe arteriolar sclerosis and ste-

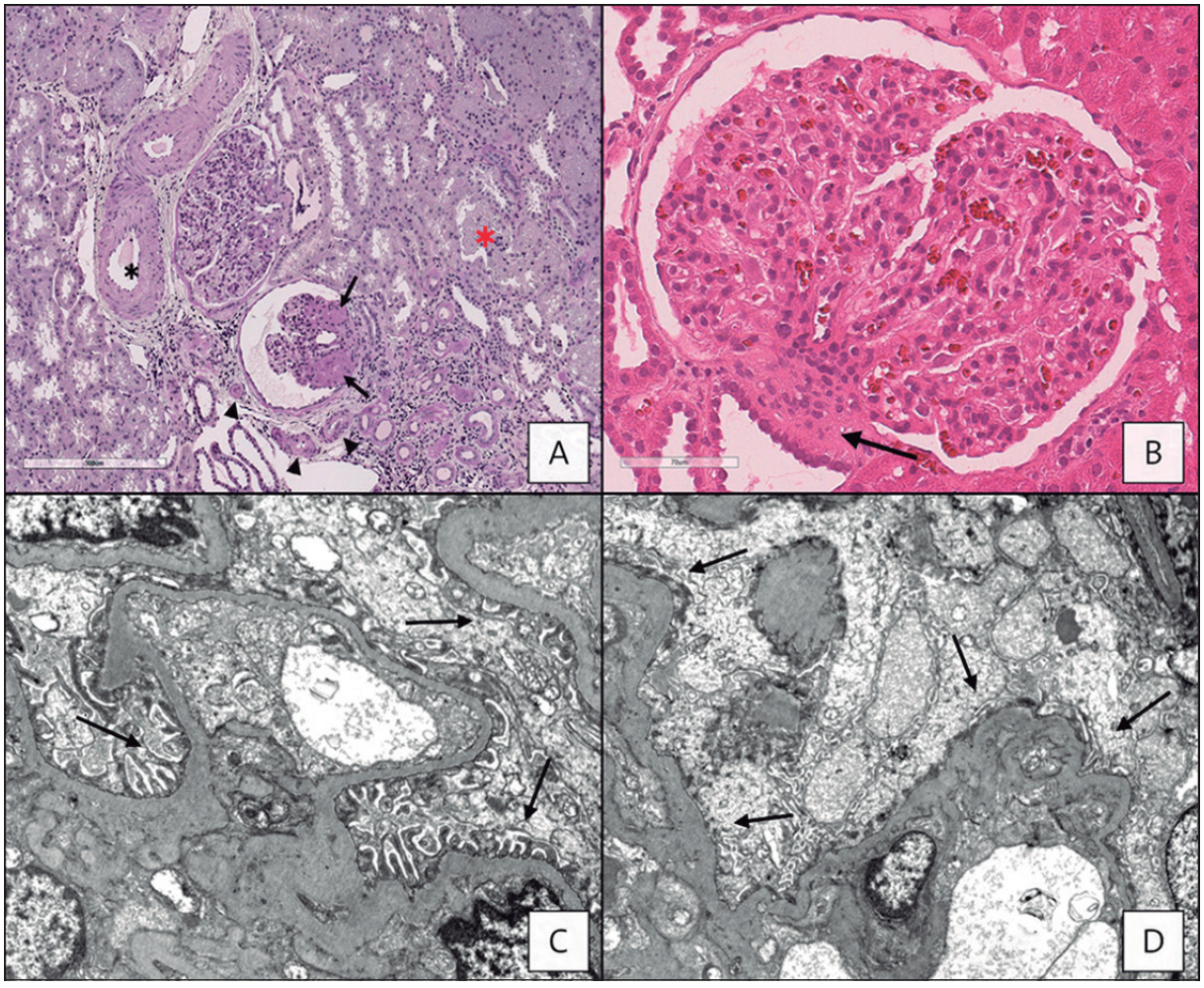


**Figure 1.** Renal biopsy of the case report. Light microscopy. A. The cortical area shows two glomeruli; the superior shows signs of hypertrophy; an interlobular arteriole with intimal sclerosis is recognized (black asterix). The lower glomerulus is located in an area of atrophic tubules and reveals an extensive segmental sclerotic perihiliar lesion (arrows). In the surrounding area an arteriolar branch with sclerosis and severe stenosis is found (arrow tips). The proximal tubules show hypertrophy characterized by increased diameter and tortuous dilatations. (red asterix) (PAS; 80X). B. Hypertrophic glomerulus with a prominent yuxtaglomerular apparatus and no segmental sclerosis (arrow) (HE; 320X). C. Electron microscopy. Segment of a glomerular tuft with capillary loops that present mostly preserved foot processes along the basal membrane (arrows) (Uranyl acetate – lead citrate, 6.000X). D. Glomerular zone that shows severe effacement of foot processes along the basal membrane in several capillary loops (arrows) (Uranyl acetate– lead citrate, 4.200X).

nosis observed in the biopsy performed 13 years later. The reduced natriuresis of oligonephronia[3] was added to the hyperactivation of the RAS.

In preterm and low birth weight infants with hypertension, blockade of the RAS with ACE inhibitors or angiotensin II receptor blockers (ARBs) is recommended for the benefits added to their systemic antihypertensive effect. RAS antagonism preferentially vasodilates the efferent arteriole, reduces glomerular hypertension, and consequently mechanical damage to the glomerular membrane and protein filtration[13,14].

It is necessary to accept the cost of the decrease in glomerular filtration rate, which is paradoxically beneficial as it slows the deterioration of renal function. It has also been postulated that the nephroprotection of ACE and ARBs includes a specific effect on podocytes, which express all the components of the RAS[15].

Recognizing the role of incomplete nephron development that leads to late kidney failure in low-birthweight preterm infants is a powerful argument for initiating early and regular prenatal checkups, which are required to reduce preterm delivery with early management of its causes.

In a national study, infectious and ischemic etiologies were the most frequent causes of preterm delivery[16]. In a public hospital in Santiago, a recent study

showed that ascending bacterial infection was the leading cause of preterm delivery, which requires routine screening and early treatment along with interventions to improve vaginal immunity[5].

Although the patient's mother did not present gestational hypertension, it is important to point out that preeclampsia increases the risk of prematurity and low birth weight by 8- and 4-fold, respectively[17], so its prevention should begin in prenatal checkups where maternal conditions associated with a higher risk of preeclampsia should be detected, since this syndrome will induce spontaneous labor or precipitate the interruption of pregnancy in the face of maternal risk and/or fetal distress; calcium supplementation when low intake is suspected[6], and initiation of low-dose aspirin at 16 weeks or earlier[6] have been shown to reduce the risk of preeclampsia. In the case of severe preeclampsia, there should be active interaction between the obstetrician and the neonatologist to decide the timing of delivery and the need to administer glucocorticoids to induce pulmonary maturation, considering that in animal models they reduce the nephron number[18].

In addition to these indications, the health care team should be sensitized about the risk of premature and low birth weight newborns in order to incorporate the follow-up recommended by Cavagnaro[1]. The joint effort to identify gestational age and birth weight when faced to proteinuria and impaired renal function in children and adolescents, along with the histological characteristics, will allow the diagnosis of focal and segmental glomerulosclerosis secondary to a developmental cause, helping to highlight the importance of prenatal programming and the subsequent follow-up.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Acknowledgments

The authors are indebted to Dr. Helmar Rosenberg†, from the Departamento de Anatomía Patológica, Facultad de Medicina Pontificia Universidad Católica, for the initial analysis of the renal biopsy.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

## References

1. Cavagnaro F. El riñón en el niño prematuro. Rev Chil Pedriatr. 2020;91:325-30.
2. Hodkin JB, Rasoulpour GS, Markowitz G, et al. Very low birth weight is a risk factor for secondary focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2009;4:71-6.
3. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens. 1988;1:335-47.
4. Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. Am J Kidney Dis. 1994;23:171-5.
5. Ovalle A, Martínez MA, Figueroa J. ¿Se puede prevenir el parto prematuro por infección bacteriana ascendente y sus resultados adversos en los hospitales públicos de Chile? Rev Chil Infectol. 2019;36:358-68.
6. Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali MM, Zavaleta N. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. Am J Obstet Gynecol. 2006;194:639-49.
7. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S. Prevention preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstet Gynecol. 2010;116(2 Pt 1):402-14.
8. Fetterman GH, Shuplock NA, Philipp FJ, Gregg HS. The growth and maturation of human glomeruli and proximal convolutions from term to adulthood: studies by microdissection. Pediatrics. 1965;35:601-19.
9. Marini MB, Rocha LP, Machado JR, Ramalho FS, Dos Reis MA, Corrêa RR. Contribution of glomerular morphometry to the diagnosis of pediatric nephropathies. Saudi J Kidney Dis Transpl. 2016;27:493-9.
10. Rosenberg H, Pulgar A, Martínez L. El glomérulo normal en donantes vivos para trasplante renal. Estudio con microscopio de luz, microscopía electrónica e inmunofluorescencia. Rev Med Chile. 1983;111:559-63.
11. Parker RA. Distribution of the changes in the juxtaglomerular apparatus in human renal artery stenosis. Nephron. 1967;4:315-25.
12. Rennke HG, Klein PS. Pathogenesis and significance of nonprimary focal and segmental glomerulosclerosis. Am J Kidney Dis. 1989;13:443-56.
13. van den Belt SM, Heerspink HJL, Gracchi V, et al. ESCAPE Trial Group. Early proteinuria lowering by angiotensin-converting enzyme inhibition predicts renal survival in children with CKD. J Am Soc Nephrol. 2018;29:2225-33.
14. Mann JFE, Hilgers KF. Renal effects of ACE inhibitors in hypertension. En Ed. Bakris GL, Elliott WJ. UptoDate, Waltham, MA. 2020. https://www.uptodate.com/contents/renal-effects-of-ace-inhibitors-in-hypertension/ última visita el 29 de agosto de 2020.
15. Liebau MC, Lang D, Bohm J, et al. Functional expression of the renin-angiotensin system in human podocytes. Am J Physiol. Renal Physiology. 2006;290:F710-19.
16. Germain AM, Carvajal J, Sánchez M, Valenzuela GJ, Tsunekawa H, Chuaqui B. Preterm labor: placental pathology and clinical correlation. Obstet Gynecol. 1999;94:284-9.
17. Shen M, Smith GN, Rodger M, White RR, Walker MC, Wen SW (2017) Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. PLoS ONE 2017;12:e0175914.
18. Fryer HJ, Welsh GI. Renal consequences of therapeutic interventions in premature neonates. Nephron. 2019;142:117-27.