

PROGRESSES IN NEONATOLOGY: IS THERE A PILOT IN THE NICU?

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WHEN THE PROGRESSES IN NEONATOLOGY LEAD TO SEVERE CONGENITAL NEPHRONS DEFICIT

«Bones can break, muscles can atrophy, glands can loaf, even the brain can go to sleep without immediate danger to survival. But should the kidneys fail, neither bones, muscles, glands nor brain could carry on.» – Homer W. Smith, *From Fish to Philosopher!* (1953)

Limits of viability in premature infants

I was recently attending a high-level scientific meeting in peri-neonatology where 50 experts from various countries discussed the recent progresses in different fields of neonatology. Several reports were devoted to very preterm infants. One of them, from the University of Iowa, USA, impressed me particularly. The title was: What are the limits of viability for extremely preterm infants? The aim of the study was to examine the outcome of infants born at 22 weeks of gestation. The results showed that all the 104 infants without active treatment died, while 26 (26%) out of 101 infants treated actively survived to discharge or were still hospitalized at 1 year. Twelve out of 19 infants who underwent evaluation at discharge had weight, length and head circumference z score of -2 or worse for age. Three infants had cerebral palsy. Five had vision impairment and one hearing defects. Neurodevelopmental impairment (NDI) was mild in five infants, moderate in 5, and severe in 9 infants (47%). The conclusion of this survey was that «the rate of active treatment of infants born at 22 weeks of gestation was increasing in the US, but that the results were not encouraging».

What about the kidney?

As the only nephrologist in the audience, I asked the question: «What about the kidneys of these premies?» The question sounded awkward. None of the doctors seemed to know that newborn infants had kidneys, and that the number of filtering units, the glomeruli, is sharply reduced in very low birth-weight neonates. The case described below illustrates the possible worrisome renal fate of those very low birth-weight infants!

Illustrative case report

At the age of 27 years, PJ presented with fatigue, pallor, malaise, nocturia, mild arterial hypertension, and proteinuria. The plasma creatinine was moderately elevated. PJ's childhood had been uneventful, except for a difficult neonatal life. He was born premature (29 weeks GA) and small for gestational age (920 g) and had presented with severe respiratory distress, transient renal failure and a patent ductus arteriosus. He had received indomethacin for closure of the ductus, and aminoglycosides to cope with the menace of infection. Thanks to effective treatment he had left the neonatal unit in good conditions, with apparent normal renal kidney function (Pcreatinine, 50 $\mu\text{mol/l}$). At the age of 3 years, the pediatrician had found normal growth (25 percentile) and normal urinalysis. The occurrence of chronic renal failure at the age of 27 years was a surprise for the patient, his parents and the family doctor. The intriguing following question was thus asked: was in this case the renal failure presenting at an early adult age already foretold at birth? We suggest that in PJ's case the following events led to chronic renal failure:

- *Intrauterine growth retardation (IUGR)*: IUGR severely affects the formation of nephrons. The lowest the birth-weight, the greatest the deficit in the number of nephrons at birth. Because nephrogenesis stops at birth in IUGR infants, the deficit remains present for life. Interestingly enough, nephrogenesis continues for 6 weeks after birth in «healthy» premature infants. Depending on their gestational age at birth, the very premature will thus also present with a congenital deficit in the number of nephrons. Such a deficit was certainly present in our patient.
- *Severe respiratory distress syndrome (RDS)*: Renal hypoperfusion with decreased glomerular filtration rate is present in neonates presenting with severe RDS. Stimulation of the renin-angiotensin system and overactivation of intrarenal adenosine mediate the renal vasoconstriction and drop in glomerular filtration rate observed in severe RDS. Prolonged renal hypoperfusion in our patient may have led to ischemic reactions at the cellular level with consequent necrosis of some nephrons, further aggravating the deficit in their number.

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- *Patent ductus arteriosus (PDA)*: Closure of the ductus was obtained by the administration of indomethacin, a non-selective COX inhibitor. The rise in renal vascular resistance induced by indomethacin must have been responsible for the occurrence of transient renal insufficiency. The late deleterious renal consequences of indomethacin have been described. Indomethacin may well have significantly impaired glomerular function and structure.

To summarize, the number of nephrons must obviously have been reduced in our patient, and a great proportion injured by the stressful conditions of perinatal life. Additional maternal causes of a nephron deficit, as described in animal studies, may also have played a role in this patient.

Maternal causes of a poor nephron endowment in the neonates

In both human neonates and experimental animals, low birth-weight, as a consequence of prematurity or intrauterine growth is associated with a decrease in the number of nephrons. In experimental animal studies, low birth-weight has also been shown to be associated with a deficit in the number of nephrons. Such a deficit has thus been demonstrated in pregnant rats or piglets fed a low protein diet; after partial ligation of the uterine artery; after feeding a low vitamin A diet; after administering aminoglycosides, aminopenicillins, cyclosporin, or glucocorticoids to the pregnant mothers; and after inducing maternal streptozotocin-diabetes. All these factors, in addition to placental dysfunction, obviously interfere with nephrogenesis.

Why does a reduced number of nephrons leads to renal failure?

A reduction in the number of nephrons has been shown to induce compensatory hypertrophy and hyperfiltration in the remnant nephrons. The increase in single-nephron glomerular filtration rate is associated with an increase in intraglomerular pressure. This response is mediated, at least in part, by the activation of the renin-angiotensin system. Angiotensin II stimulates postglomerular vasoconstriction, as well as various growth factors and cytokines. Hyperfiltering glomeruli are prone to develop glomerulosclerosis. The first manifestation of glomerular suffering is the occurrence of microalbuminuria and proteinuria. Glomerulosclerosis ultimately leads to progressive terminal chronic renal failure and arterial hypertension.

Protection of the hyperfiltering kidney

Because angiotensin II appears to play a key role in the adaptive changes that ultimately result in glomerulosclerosis and progressive renal failure in patients with a reduced number of nephrons, it appeared rational to protect the hyperfiltering kidney by the administration of angiotensin II inhibitors or antagonists. They indeed proved effective. In our patient, they significantly reduced the rate of progression of renal failure. But we know that this protection will not last forever. His plasma creatinine is steadily increasing, and the need for dialysis support in the future is certain.

When to start nephroprotection in low birth-weight infants?

Ideally, nephroprotection should start early, before the onset of significant glomerular injury. But nobody will be really pleased to start the administration of angiotensin inhibitors or antagonists before having evidence of the renal suffering. Angiotensin II is indeed an important growth factor, the inhibition of which may really not be safe in the early phases of development. The truth is that for the time being, there is no real safe effective protection of the kidney of very low birth-weight infants.

Conclusion 1

Because of a deficit in nephrons endowment at birth, extremely low birth-weight infants are prone to develop progressive renal failure at an early age!

Conclusion 2

Can we simply continue to fight for the survival of extremely low birth-weight infants, knowing that a great proportion of them will develop renal insufficiency at an early age ... in addition to their neurodevelopmental deficits! Would it not be preferable to discuss the overall consequences of extreme prematurity, and define a consensus on reasonable limits of viability. The NICU is like a plane! It needs a pilot able to take into account all aspects of prematurity!

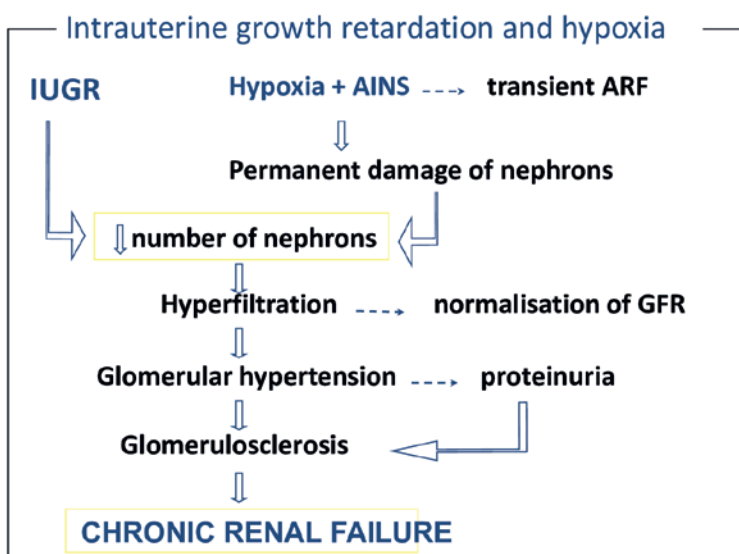


Figure 1: The pathogenesis of chronic renal failure in very low birth-weight infants

AINS: anti-inflammatory non-steroidal drugs / ARF: acute renal failure / GFR: glomerular filtration rate

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