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Original Research Article

Risk factors for acute neonatal renal failure

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ABSTRACT

Background: Acute neonatal renal failure is a health problem. Its risk factors and its clinical and evolutionary profile remain unknown in the Malagasy context. The main objective of this study was to determine its risk factors.
Methods: This was a 14 month, single-center, retrospective, case-control study (November 2018 to December 2019). The cases were represented by newborns hospitalized and presenting an hypercreatininaemia (value >133 µmol/l or according to the KDIGO criteria) and controls by neonates without an hypercreatininaemia. One case was matched to 2 controls.
Results: We included 75 cases. The prevalence was 14.5%. The mean age was 5±6.78 days (p=0.006). The sex ratio was 1.27. The mean gestational age was 36.69±3.84 WA (p=0.66). The mean serum creatinine value was 180.32 µmol/l. Thirty-one newborns had died (41.3%). The risk factors were: sepsis (OR=9.37, p≤0.001, CI=3.03, 33.5), perinatal asphyxia SARNAT 2 (OR=4.52, p=0.007, CI=1.53, 13.8) and SARNAT 3 (OR=7.90, p=0.021, CI=1.56, 60.4), increased weight loss (OR=4.04, p=0.006, CI=1.51, 11.2) and respiratory distress (OR=2.76, p=0.005, CI=1.37, 5.77).
Conclusions: The risk factors were consistent with the data in the literature. Better management of parturients and the newborn as well as monitoring of serum creatinine in hospitalised newborns are recommended.

Keywords: Acute neonatal renal failure, Perinatal asphyxia, Risk factors, Sepsis

INTRODUCTION

Acute renal failure is defined by a sudden cessation of renal function leading to the inability of the kidneys to excrete the waste products of nitrogen metabolism and to maintain the hydro-electrolyte balance of the body. It results in a rise in serum creatinine and in half of the cases by oliguria or even anuria.[1-3]

It represents a major health problem in newborns because: its incidence is high in the neonatal period (unlike in children) and more particularly in newborns admitted to an intensive care unit.[4] Indeed, during the first days of life, newborns are more at risk of developing renal failure due to low glomerular filtration rate, high renal vascular resistance, low perfusion of the cortical region, and high tubular sodium excretion.[3,5-7] In addition, the evolution of neonatal acute renal failure is often pejorative due to high short-term mortality and the increased risk of occurrence of renal sequelae including long-term chronic renal failure.[2-4,6,8-14]

We do not currently have sufficient data in Madagascar to determine its risk factors. In addition, the epidemiological, clinical and short-term evolutionary profiles of this pathology remain locally unknown.

The main objective of this study was therefore to determine the risk factors for the occurrence of acute renal failure in newborns and secondarily to describe the

epidemiological, clinical and short-term evolutionary profile in the Malagasy context.

METHODS

This was a retrospective analytical case-control study, over a period of 14 months from 01 November 2018 to 31 December 2019 and carried out at the University Hospital Center Mother and Child, Tsaralalana, Madagascar and particularly in the neonatology department.

Cases were defined as all newborns hospitalized and presenting an increase in serum creatinine (taken beyond the 12th hour of life) defined either: by a value >1.5 mg/dl (or 133 µmol/l) on a single dosage or according to the kidney disease improving global outcome (KDIGO) criteria.

Controls were defined as newborns hospitalized in the neonatology department during the study period and not presenting an increase in serum creatinine.

Matching was done according to chronological age (slices of days of life) and gender with a ratio of 2 controls for 1 case.

The following were not included in the study: newborns seen in consultation and not hospitalized and any child over 28 days old. Were excluded from the study the incomplete files and not presenting a dosage of creatinine.

The data was entered anonymously into a database designed using Microsoft excel software. Statistical analysis was performed on R software. The strength of association between a dependent variable and an independent variable was assessed by calculating the odds ratio.

A value of $p<0.05$ was considered significant. The risk factors with a value of $p<0.25$ were secondarily evaluated by a multivariate analysis by logistic regression.

RESULTS

During our study period, there were 517 admissions of newborns in the neonatology department. According to the inclusion criteria, 75 newborns presented acute renal failure. The incidence was therefore 14.5%.

The characteristics of the newborns are described in Table 1. The mean age was 5±6.78 days (p=0.006). Thirty newborns were premature (40%), and 45 were full term (60%). The mean birth weight was 2598±796 grams (p=0.60).

The main reason for admission was neurological (40 cases or 53.3%, p=0.02). It should be noted that 26 newborns (34.66%) had more than one reason for admission (Table 2).

The mean serum creatinine value was 180.32 µmol/l.

The most frequent etiological diagnoses were: infections (61 cases or 81.3%), perinatal asphyxia (25 cases or 33.3%), growth retardation in utero (24 cases or 32%) and dehydration (16 cases or 21.3%). It should be noted that 45 newborns (60%) had more than one etiological diagnosis.

The average duration of hospitalization was 8±7.67 days (p=0.007479). The minimum duration was 1 day and the maximum duration was 34 days. Thirty-one newborns had died (41.3%).

Table 1: Characteristics of newborns.

Variable	N	Percentage (%)
Gender		
Female	33	44
Male	42	56
Sex ratio	1, 27	
Age of newborns at admission (days)		
0-7	53	70,6
8-15	16	21,3
16-21	3	4
22-28	3	4
Gestational age (weeks)		
22-28	6	8
28-32	3	4
32-37	21	28
>37	45	60
Low birth weight <25000 g	22	29,33
Small gestational age	24	32
Vaginal delivery	69	92
Caesarean	6	8

The risk factors were: septic shock with an OR=9.37, 95% CI [3.03,33.5] ($p\leq0.001$), perinatal asphyxia SARNAT 2 with an OR=4.52, 95% CI [1.53, 13.8] (p=0.007), and SARNAT 3 with an OR=7.90, 95% CI [1.56, 60.4] (p=0.021), increased weight loss with an OR=4.04, 95% CI [1.51, 11.2] (p=0.006) and respiratory distress with an OR=2.7695% CI [1.37, 5.77], (p=0.005) (Tables 2-4).

Table 2: Reasons for admission (cases).

Reasons for admission	N (%)	P value
Neurological	40 (53.3)	0.02
Respiratory*	19 (25.3)	0.144
Weight gain disorders	15 (20)	1
Fever	11 (14.6)	1
Jaundice	9 (12)	0.43
Other**	12 (16)	0.43

*Breathing difficulty, gasp-like breathing, cyanosis, apnea, cough, rhinorrhea; **reference for prematurity, reference for asphyxia, inguinal hernia, anuria, haematuria, umbilical haemorrhage

Table 3: Neonatal risk factors.

Variable	OR (IC95%); p value	aOR*(IC95%); p value
Early neonatal bacterial infection	2.05 (1.16-3.61); 0.01	0.92 (0.36-2.40); 0.9
Septic shock	15.38 (5.60-42.26); 4.875e-10	9.37 (3.03-33.5); <0.001
Late neonatal infection	0.59 (0.32-1.09); 0.12	0.75 (0.29-1.94); 0.5
Nosocomial infection	0.86 (0.33-2.19); 0.93	-
Perinatal asphyxia	2.62 (1.37-5.02); 0.0051	
Perinatal asphyxia SARNAT 1	0 (0.0-0.62); 0.0054	0.00; >0.9
Perinatal asphyxia SARNAT 2	2.69 (1.06-6.81); 0.056	4.52 (1.53-13.8); 0.007
Perinatal asphyxia SARNAT 3	16.77 (3.68-156.2); 6.998e-06	7.90 (1.56-60.4); 0.021
Increased weight loss	3.08 (1.40-6.76); 0.006	4.04 (1.51-11.2); 0.006
Respiratory distress	1.85 (1.05-3.2); 0.04	2.76 (1.37-5.77); 0.005
Vaginal delivery	1.76 (0.67-4.61); 0.33	-
Birth outside health centre	1.65 (0.92-2.96); 0.11	1.54 (0.73-3.22); 0.3
Congenital heart disease	0.79 (0.07-5); 1	-
Low birth weight	1 (0.54-1.83); 1	2.63 (0.48-13.9); 0.3
Prematurity	1.50 (0.84-2.68); 0.21	1.24 (0.57-2.68); 0.6

Table 4: Maternal risk factors.

Variable	OR (IC95%); p value	aOR*(IC95%); p value
Maternal disease	3.73 (0.91-17.98); 0.04	2.60 (0.50-16.1); 0.3
Maternal medication during pregnancy	2.76 (0.60-12.66); 0.342	-

DISCUSSION

The hospital prevalence of acute renal failure in newborns is poorly known because the majority of published studies are monocentric with variable sample sizes.[15-22] Data found in Middle Eastern countries like India and Pakistan indicate a prevalence that varies between 1.54% and 10.8%. In France, it is estimated between 3 and 10%, which is two times lower than that found in the Anglo-Saxon literature (United States) which is 8 to 24%.[1,4] The high prevalence probably reflects less effective management of the "parturient-newborn" couple compared to other countries, due to an insufficient technical platform but also due to unfavorable socio-economic factors.

The majority of studies find an average age of less than 14 days.[16-21,23] The result of the study is similar to those found by the studies of Stavik carried out in India in 2008 (5.22 days) and by that of Nariman carried out in Iraq in 2011 (5.26 days).[17,21] The early onset during the first days of life of renal failure in newborns is explained by a greater sensitivity of the kidney to hypoperfusion. Indeed, the kidneys receive only 2.5 to 4% of cardiac blood flow at birth (with low cortical perfusion). In addition, the glomerular filtration rate is low during the first days of life, around 10 to 20 ml/min/1.73 m^2. Hypoperfusion is also favored by high plasma renin activity.[3,5-7,24]

The male predominance found in the study is in agreement with that found in most of the published studies.[15,17,19-22,25] The reason for this predominance can be explained by a greater susceptibility of boys to perinatal distress such as sepsis and respiratory distress.[15] The average gestational age found in the study is lower than that of the literature, which is 37 weeks.[17,21]

The reasons for neurological and respiratory admission are frequently associated with infectious pathologies and perinatal asphyxia. Thus, the asphyxiated newborn is frequently hypotonic and hyporeactive at birth with a low Apgar score.[26] In addition, multiple organ failure and neonatal encephalopathy (classified according to the Sarnat classification) are frequent complications of perinatal asphyxia.[26] Coulibaly reported that renal failure was frequently observed in neonates admitted for coma and diagnosed with perinatal asphyxia (p=0.020).[27] A similar study by Nouri demonstrated that 27% of patients with renal failure experienced seizures and 60% respiratory distress.[28] According to the recommendations of the French Society of Neonatology (FSN) in 2017, the presence of clinical signs including respiratory distress and neurological signs in the first 48 hours of life should suggest the occurrence of an early neonatal bacterial infection.[29]

The mean serum creatinine value is lower than those found by the majority of studies: Mortazavi (350±211.2 µmol/l), Nariman (299.2±132 µmol/l), Agras (228. 8±202.4 µmol/l), Naveed (265.7±155.7 µmol/l) and Halder (246.4±110 µmol/l).[15,17,19,20,22]

The average duration of hospitalization found in the study is lower than those found by Momtaz in 2011 (12.6±1.0 days), by Zulik in 2015 (10.2±3.2 days), and by Ghobrial in 2015 (24.6±13.3 days).[16,23,30] The reason for this shorter duration is explained by a large number of early deaths occurring before the 7th day of life (27 cases or 36%). The

mortality rate is similar to those found by Youssef in 2015 (44.4%).[18] Nevertheless, it remains higher than the majority of mortality rates found in other studies.[15-17,19-23] This high rate is explained by the absence of extra-renal purification treatments such as peritoneal dialysis.

Late neonatal infection and nosocomial infection were not risk factors unlike early neonatal bacterial infection and septic shock. Multivariate analysis by logistic regression showed that only septic shock was a risk factor (OR=9.37, p<0.001). This finding could be explained primarily by the fragility of the neonatal renal vasculature during the first week of life.[3,5-7,24] Secondly, late neonatal infections were represented by viral infections (rhinitis and moderate bronchiolitis) of lesser severity for the vital prognosis, thus minimizing the risk of occurrence of renal failure. Thirdly, the number of nosocomial infections was low (7 observations or 9.3% in cases against 16 observations or 10.67% in controls). Several studies point out that septic shock is one of the main risk factors for the occurrence of acute renal failure. Its incidence in these studies varies between 28.5% and 77.5%.[15-20,22,23,25] Four authors found a significant association between septic shock and renal failure: Stavik et al with an OR=14.46 (p<0.001), Marthur (p<0.001), Jagrawal (p<0.001) and Holda (p<0.001).[21,31-33] The occurrence of renal failure following septic shock is due to several pathophysiological mechanisms. The most evoked mechanism remains renal hypoperfusion, which results from both hypovolemia, ischemia by septic embolism and inflammation.[34-36]

Multivariate analysis by logistic regression demonstrated a correlation between the severity of anoxic-ischemic encephalopathy and the risk of occurrence of acute renal failure. Perinatal asphyxia is, after septic shock, the second cause of renal failure in newborns.[2,3,6,8,10,11] In this context, the kidney remains the most affected organ after the brain. The occurrence of renal damage is correlated with the severity of the neurological damage. Renal failure results from renal hypoperfusion, itself induced by hypoxia.[26-28] The incidence found in the study (33.3%) is similar to those found by Mortazavi (29.8%), Agras (40%), Stavik (32.43%), Zulic (42.8%).[15,19,21,23] Gupta found in a case-control study, a significant increase in the mean values of uraemia (p≤0.001) and creatinine (p≤0.001) in the group of asphyxiated newborns compared to the group witnesses.[37] Finally, Alaro studied a cohort of 60 asphyxiated newborns born at term in Kenya and estimated at 15 the relative risk (p=0.034) of occurrence of renal failure in newborns presenting with anoxic encephalopathy -ischemic stage 3 according to the Sarnat classification.[38]

The majority of children who showed increased weight loss (16 cases out of 17) also presented hypernatremia, thus producing dehydration. According to descriptive studies, dehydration is rarely implicated in the occurrence of renal failure and no analytical data confirms its involvement as a risk factor.[15,18,20,22] According to Agras, dehydration results from inadequate exclusive breastfeeding.[19]

The incidence of prematurity differs according to the studies (between 3.3% and 66.7%).[15-23,25,30] Our finding is in line with those of Stavik and Ghobrial, who argued that newborns born at term were at greater risk of developing renal failure (respectively p=0.001 and p=0.456).[21,30] This finding could be explained by the fact that the majority of newborns diagnosed with sepsis and/or perinatal asphyxia were full term newborn.

The literature identifies respiratory distress as one of the main risk factors for renal failure.[8,10] Its incidence remains high in the majority of descriptive studies (between 25.2% and 55.6%).[15,16,18,23] Nevertheless, the 2 analytical studies carried out by Stavik and Ghobrial did not find a significant association with the occurrence of acute renal failure (respectively p=0.004 and p=0.541).[21,30]

The pathophysiological mechanism of respiratory distress is similar to that of perinatal asphyxia leading to hypoxia and thus renal hypoperfusion.

Stavik objectified that delivery performed outside a health center as being a risk factor (p=0.011).[21] The fact of giving birth outside the hospital can expose you to perinatal complications due to the lack of supervision by a qualified medical team, by the absence of a sufficient technical platform but also by the risk of a delay in support related to a late transfer. In the study, the definition of birth outside of a health center included births at home, in doctors' offices and in midwives' offices. Giving birth in a hospital could reduce the risk of medical complications for the mother and the newborn.

Limitations

The retrospective nature of our study did not allow us to be entirely exhaustive in the collection and interpretation of certain data including antenatal ultrasound (amount of amniotic fluid, which is a reflection of kidney function, and the existence of possible renal malformations like valves of the posterior urethra, renal polycystosis, dysplasia and renal hypoplasia). Several newborns were unable to perform a serum creatinine assay due to pecuniary problems or due to an intra-hospital death having occurred before the realization of a creatinine. The monocentric aspect of the study and the small size of the sample limit interpretation and extrapolation of results in the general population.

CONCLUSION

Renal failure is a worrying pathology in newborns. It is often marked by significant morbidity and remains a risk factor for mortality in its own right. Its origin is multifactorial. The multivariate analysis confirms that perinatal asphyxia, including those associated with encephalopathy classified as SARNAT 2 and 3, septic

shock, increased weight loss and respiratory distress are the main risk factors. These risk factors are consistent with those found in the literature and may be intertwined. They testify to the association between the increasing severity of the pathology and the risk of occurrence of renal failure in the newborn.

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