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ORIGINAL ARTICLE

Hyponatremia in children under 100 days old: incidence and etiologies

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Abstract

Hyponatremia is one of the most common electrolyte disorders in hospitalized children. The underlying mechanisms are poorly understood and potentially multifactorial, making management difficult, particularly in neonates. This retrospective study aimed to determine the incidence and etiologies of hyponatremia in hospitalized children under the age of 100 days, in our pediatric tertiary care hospital over a 1-year period. The etiology of hyponatremia was determined by reviewing the data noted in each patient's medical reports. Neonatal hyponatremia had a prevalence of 4.3% (86/2012 patients) and was mostly hospital-acquired (74/86 patients). Fifty-nine patients (68.9%) were preterm neonates. The etiology was iatrogenic in 26 cases (30.2%). In other cases, hyponatremia was due to transient (23 patients, 26.7%) or genetic abnormalities of the renal mineralocorticoid pathway (3 patients, 3.4%), SIADH (12 patients, 14%), digestive disease (3 patients, 3.5%), acute renal failure (3 patients, 3.5%), or heart failure (1 patient, 1.2%).

Conclusion: Our findings confirm that hyponatremia is a frequent electrolyte disorder in neonates. Various mechanisms underlie this condition, most of which could be prevented by optimized management. The prevalence of genetic hypoaldosteronism and pseudohypoaldosteronism was higher than expected. We provide a simple diagram to help physicians identify the mechanisms underlying neonatal hyponatremia.

What is Known:
- *In neonates, hyponatremia may be multifactorial, making it difficult to treat.*
- *Newborns display partial resistance to aldosterone, and preterms have a defect in aldosterone secretion.*

What is New:
- *Four percent of hospitalized neonates had hyponatremia, 86% hospital-acquired. Hyponatremia was due to a transient or constitutional defect of the mineralocorticoid pathway in 26/86 patients (30%) which is higher than expected.*
- *We propose a tree diagram for improving the management of hyponatremia in neonates.*

Keywords Hypo-osmolality · Mineralocorticoid signaling pathway · Newborns · Prematurity · Salt-wasting

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Introduction

Hyponatremia is one of the most common electrolyte disorders in hospitalized children [31], and its early diagnosis and management are crucial to prevent morbidity and mortality [2]. Hospitalized children with hyponatremia have worse outcomes than hospitalized children with normal serum sodium concentration [5, 7, 14, 17], and morbidity and mortality are higher due to the severity of the underlying conditions. Hyponatremia is often asymptomatic, especially in neonates, who only rarely show symptoms of cerebral edema, due to the deformability of the neonatal skull. However, neonatal patients may present neurological symptoms, including seizures, if plasma sodium concentration decreases rapidly [6, 9, 15, 27]. Identification of the mechanism underlying hyponatremia is essential, to ensure effective patient care and to prevent the deterioration of fluid and electrolyte balance.

Serum sodium concentration determines intracellular hydration and is controlled by osmoreceptors and vasopressin. The amount of sodium present in cells is determined by the mineralocorticoid pathway. Sodium is the principal cation in the human body, and it is crucial for the extra- and intracellular environments to have the same osmotic pressure. Hyponatremia may arise through two mechanisms, both resulting from a primary excess of ADH. The first of these mechanisms is hypovolemia (with sodium depletion or retention), leading to a decrease in blood flow, with ADH secretion triggered when extracellular volume decreases by at least 10%. The second mechanism involves the inappropriate secretion of ADH (SIADH), mostly due to pulmonary diseases. A third possible mechanism is hospital-acquired hyponatremia due to excess primary water as a result of inadequate intravenous hydration. During the first few months of life, the renal tubule is immature, and newborns consequently display partial resistance to aldosterone, resulting in physiological weight loss during the first few days of life. This lack of hormone responsiveness is due to a large decrease in mineralocorticoid receptor expression in the distal parts of the nephron [19]. Due to this transient aldosterone resistance, the reference values for serum sodium concentrations are lower and those for serum potassium are higher during the first few weeks of life. In preterm infants, urinary sodium loss is even greater, due to both renal and adrenal immaturity [20].

Hyponatremia can result from persistent urinary sodium loss, which may have various causes: renal organic tubulopathies, adrenal insufficiency, isolated mineralocorticoid deficiency, congenital pseudohypoaldosteronism [25, 26, 30, 34], transient pseudohypoaldosteronism secondary to pyelonephritis [12, 23, 30], and functional tubulopathy due to preterm birth [3], all of which can arise during the first few weeks of life. In patients under the age of 3 months, hyponatremia may be multifactorial, making it difficult to determine the underlying mechanisms. We conducted a retrospective single-center study in a pediatric tertiary care hospital, to assess the incidence of hyponatremia in infants under the age of 100 days and to evaluate the various mechanisms leading to water and sodium imbalance. We propose a new tree diagram for improving the management of these patients.

Patients and methods

Patients

All children under the age of 100 days, hospitalized at Robert-Debré Hospital, Paris, France, who had at least once one serum sodium concentration determination between January 1 and December 31, 2012, were screened, via the hospital electronic medical system. Hyponatremia was defined according to the patient's age: < 130 mmol/l for children aged less than 31 days and < 133 mmol/l for children aged from 32 to 100 days. The lowest value was considered for patients with several low serum sodium concentrations.

The exclusion criteria were the following: contamination of the blood sample with intravenous solution, hyperglycemia or known hypertriglyceridemia (i.e., serum sodium concentration not reflecting plasma osmolarity), and the impossibility of retrieving data from the patient's medical records. In addition, we recorded serum sodium concentrations that were performed before and after the episode of hyponatremia (kinetic), to exclude bias due to lab error.

This retrospective observational study was reviewed and approved by the local ethical review committee for biomedical research (No. 2015/172) and by the French data protection authority (CNIL No. 1827596), in accordance with the Declaration of Helsinki.

Data collection

We collected data concerning the patients' clinical and biological characteristics from their medical reports, with a view to determining the etiology of hyponatremia. The collected data included demographic parameters (sex, age at admission, age at the trough hyponatremia), personal medical history (preterm birth, intra-uterine growth retardation (IUGR) defined as a birth weight below the 10th percentile according to Audipog curves [18], congenital malformation or disease), family medical history (e.g., deaths during childhood, adrenal insufficiency, consanguinity), information about hospitalization (cause, hospital department, duration), clinical events occurring on the days preceding hyponatremia (e.g., weight changes just before and after the occurrence of hyponatremia sepsis, pulmonary infection, hemodynamic failure, renal, gastrointestinal or neurological disorders, surgery), ongoing treatments (diuretics, intravenous solutions), and status at discharge.

Biological data were also collected to facilitate the interpretation of serum sodium concentration: plasma electrolytes (potassium, bicarbonates), glucose, albumin and protein concentrations, renal function (urea, creatinine), and urinary electrolyte concentrations (sodium, potassium, creatinine). Highly hemolyzed samples were excluded from the study. Moderately hemolyzed samples (according to the colorimetric index LIH OSR62166, Beckman Coulter, Inc., France) were not considered for the potassium concentration analyses. Plasma osmolarity was calculated as follows: [sodium (mmol/l) × 2 + glycose (mmol/l) + urea (mmol/l)] [33]. All plasma biological dosages were performed from venous blood samples. When available, the results of the urinary cytobacteriological examination and renal ultrasound were also collected. Finally, if hormonal tests had been performed, we obtained the results of plasma renin, aldosterone, 17hydroxyprogesterone (17OHP), adrenocorticotropic hormone (ACTH), and cortisol determinations.

Determination of the etiology of hyponatremia

For each patient, the clinical and biological data were reviewed to determine the cause of hyponatremia. The diagnosis was based on published recommendations (Supplemental Table 1) [3, 8, 10, 13, 19, 23, 28, 29]. For patients with central nervous system disorders, we intentionally did not separate SIADH from the cerebral salt-wasting syndrome, because of the overlap between these two diagnoses, which differ principally in effective arterial blood volume [24]. Our patients with severe central nervous system disorders had suffered anoxo-ischemia (2 patients). In this very specific situation, the failure of other organs may have modified effective plasma volume, making it even more difficult to differentiate between these two etiologies.

Statistical analyses

Statistical analyses were performed with Prism 6 software (GraphPad Software, Inc., San Diego, CA). Unless otherwise specified, all values are expressed as mean ± standard deviation. Variables with a large distribution are expressed as medians ± interquartile ranges (Q3–Q1).

Results

We found that 92 (4.6%) of the 2012 eligible patients under the age of 100 days had presented an episode of hyponatremia. Six of these patients were excluded: two due to contamination with intravenous solution, two due to hyperosmolar hyponatremia because of major hyperglycemia, and two because medical records were incomplete (see flow chart in Fig. 1). Eighty-six patients (4.3%) presenting an episode of hyponatremia were thus eligible for the study.

Population

These 86 patients comprised 54 boys (62.7%) and 32 girls (37.2%). Fifty-nine of the children (68.9%) were preterm neonates born at a mean gestational age of 27.5 ± 4.0 weeks of gestation. Twenty patients from the total population (22.9%) were the result of multiple pregnancies and 14 (16.2%) had IUGR. Most patients ($n = 68$; 78.2%) were initially transferred from another department or another hospital (Table 1) and

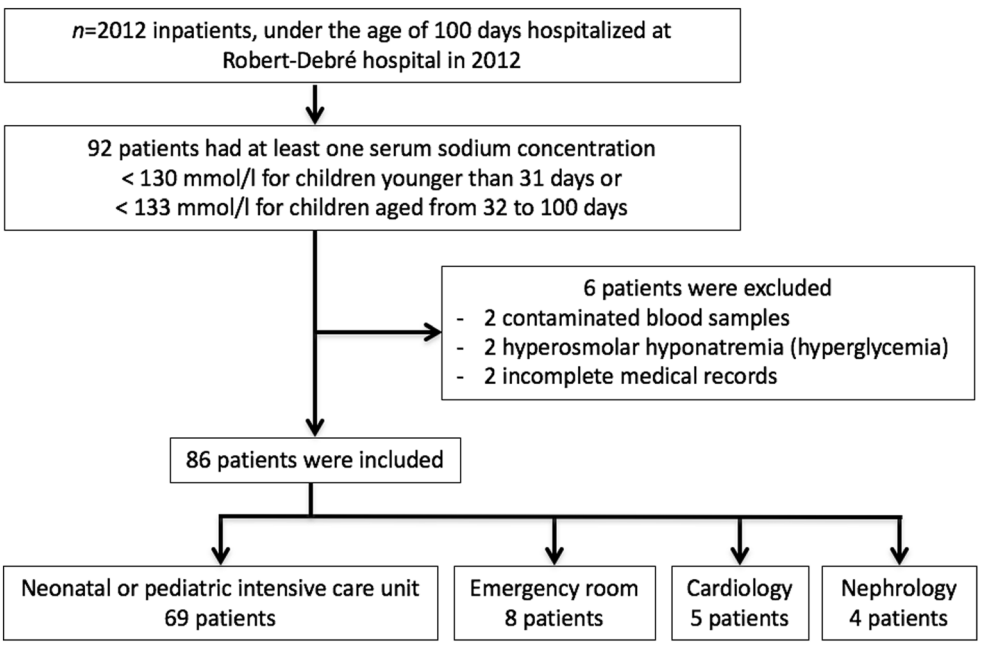

Fig. 1 Flow chart, indicating the department in which the lowest value for natremia was recorded for the patients included in this study

were admitted to the medical department in which the episode of hyponatremia occurred at a median age of 4.5 days. At the time of hyponatremia, most patients ($n = 69$; 80.2%) were in either a neonatal intensive care unit (NICU) or a pediatric intensive care unit (PICU) (Fig. 1). However, hyponatremia alone (without complication) was never a sufficient reason for transfer to the intensive care unit in any of these cases.

Kinetics of hyponatremia

Median age at the detection of hyponatremia was 19.5 days (IQR 9.25–44.75) for term infants and 17.0 days (IQR 8.5–36.0) for preterm neonates. The lowest serum sodium concentration value was obtained 4 days (IQR 1–12) after admission and only 12 patients (14.0%) had hyponatremia on admission to hospital; all the other patients (74; 86.0%) had hospital-acquired hyponatremia. A normal serum sodium concentration obtained before the onset of hyponatremia was available for 65 patients (75.5%), and these measurements were obtained with a median of 1.0 day (IQR 1–3) before the episode of hyponatremia.

Serum sodium concentrations ranged from 109 to 132 mmol/l. In 28 patients (32.5%), serum sodium concentrations fell below 125 mmol/l, and in seven patients (8.1%), these concentrations were below 120 mmol/l. Six of the seven patients with severe hyponatremia (serum sodium concentration below 120 mmol/l) were below the age of 1 month (Fig. 2).

In most cases, no clinical manifestation that could be attributed exclusively to hyponatremia was detected. Only one patient presented hyponatremia-related seizures, which were a consequence of SIADH secondary to respiratory syncytial virus bronchiolitis. In this patient, sodium serum concentration decreased to 124 mmol/l and seizures were the reason for transfer to the intensive care unit.

Table 1 Characteristics of the patients under 100 days of age presenting an episode of hyponatremia during 2012 at Robert-Debré Hospital

	Patients ($n = 86$)	Range
Demography		
Boys/girls (*n*)	32/54 (37.2%/62.7%)	–
Age at admission (d)	20.3 ± 27.0	0–98
Age at hyponatremia (d)	29.4 ± 25.4	1–98
Birth		
Multiple pregnancy (*n*)	20 (22.9%)	–
Premature birth	59 (68.6%)	
IUGR (*n*)	14 (16.2%)	
Hospitalization		
Patient provenance (*n*)		
Home (*n*)	17 (19.8%)	–
Other department (*n*)	68 (78.2%)	–
Reason for admission (*n*)		
Preterm birth	34 (39.5%)	–
Fever	12 (14.0%)	–
Vomiting	10 (11.6%)	–
Failure to thrive	18 (20.9%)	–
Dehydration	8 (9.3%)	–
Respiratory distress	25 (29.1%)	–
Duration of stay in the department (d)	42.1 ± 47.7	0–233

n number, *d* days

Mechanisms underlying hyponatremia

The mechanisms underlying hyponatremia are shown in Fig. 3, classified as described in Supplemental Table 1. Iatrogenic mechanisms were involved in 26 cases (30.2%), with diuretic treatment implicated in 17 patients and hypoosmolar intravenous fluid therapies in four patients.

Hyponatremia was caused by a transient or constitutional defect of the mineralocorticoid pathway in 26 patients (30.2%): it was due to tubular immaturity in 19 patients (22.0%), transient (4 patients, 4.7%) or primary (2 patients 2.3%) pseudohypoaldosteronism in six patients, and primary hypoaldosteronism in one patient (1.2%). One of the patients with a genetic defect of the mineralocorticoid pathway had aldosterone synthase deficiency due to a homozygous mutation of the *CYP11B2* gene and two had heterozygous inactivating mutations of the mineralocorticoid receptor gene, *NR3C2*.

The cause of hyponatremia was SIADH in 12 patients (14%, including 6 patients with bronchiolitis), digestive in three patients (3.5%), acute renal failure in three patients (3.5%) and heart failure in one patient (1.2%).

In 26 patients (30.2%), hyponatremia was considered to have a multifactorial etiology, including iatrogenesis (11 patients; 12.7%).

Mean serum sodium, potassium, and bicarbonate concentrations differed significantly between the underlying mechanisms of hyponatremia (Fig. 4). Hyponatremia due to a defect of the mineralocorticoid pathway was more severe than hyponatremia due to iatrogenesis ($p = 0.0053$). Serum bicarbonate concentrations were significantly lower in cases of hyponatremia due to mineralocorticoid pathway defects than in cases of hyponatremia of all other etiologies except for mixed etiologies.

Patient outcomes

Even before the occurrence of hyponatremia, a large proportion of the patients were in a severe clinical condition, and 12 patients (14.0%) died. None of these deaths were directly linked to the episode of hyponatremia, and all occurred in the NICU or PICU. Nine of these 12 patients (75.0%) were preterm infants. Death occurred a median of 12 days (IQR 3.25–28.25) after the episode of hyponatremia. In six of these

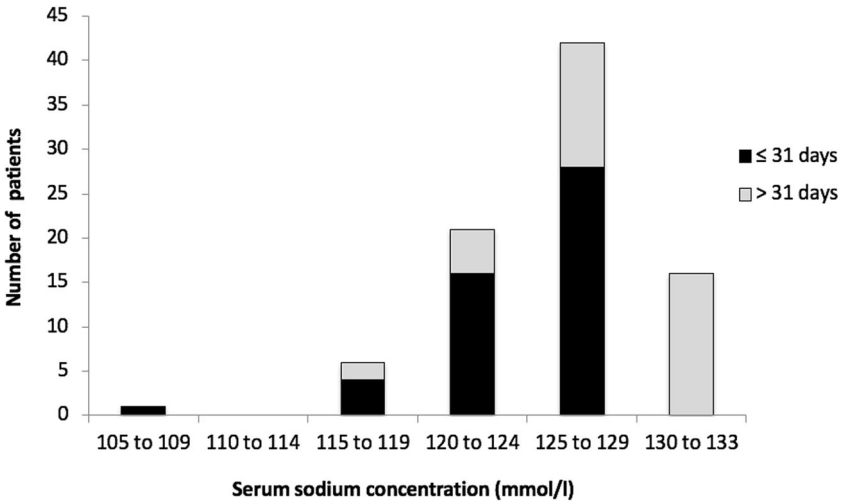

Fig. 2 Distribution of the lowest values for serum sodium concentration, as a function of patient age at the time of hyponatremia

patients (50.0%), serum sodium concentration had decreased below 125 mmol/l.

Discussion

This is the first study to describe the prevalence and etiologies of hyponatremia in neonates. Compared with older children, infants below the age of 100 days have a higher risk of hyponatremia due to several mechanisms.

In 2012, 4.3% of the inpatients under the age of 100 days at Robert-Debré Hospital presented hyponatremia, which was hospital-acquired in 86.0% of these cases. Mortality (14.0%) was higher among patients with hyponatremia than among patients of the same age without hyponatremia hospitalized at Robert-Debré Hospital in the same year (2.3%).

Our study has several limitations. First, it is a retrospective single-center study. The clinical data were collected from the patients' medical reports, on which some data relevant for the interpretation of serum sodium concentrations and their variation might have been missing. In addition, the distribution of etiologies reported here reflects the recruitment of patients at Robert-Debré Hospital, which has both a NICU and a PICU (supporting very preterm newborns), and many specialist departments, such as nephrology treating patients with fluid and electrolyte disorders. The distribution of etiologies obtained would probably be different in a hospital with a single general pediatric department.

On the plus side, the systematic review of serum sodium concentrations performed with the hospital medical information system made it possible to ensure that recruitment was exhaustive. Only two of 92 patients (2.3%) could not be included because essential clinical information was missing. Moreover, the inclusion period extended over a 12-month period, making it possible to avoid recruitment bias due to seasonal infectious diseases, such as viral bronchiolitis.

Our results confirm the findings of previous studies [14, 31]. Several different etiologies were identified and hyponatremia might have been avoided in a number of cases, had management been optimized. Iatrogenic causes played a particularly large role in the occurrence of hyponatremia. Diuretics and hypotonic intravenous solutions were the main iatrogenic causes of hyponatremia. As previously suggested, the use of hypotonic solutions should be avoided, notably

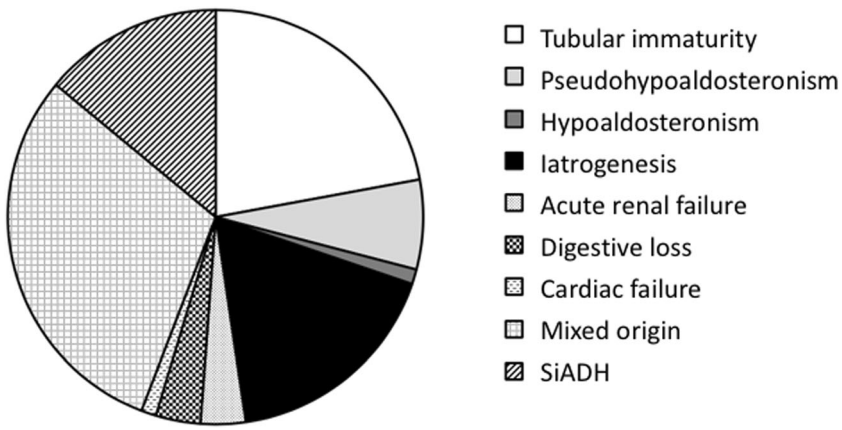

Fig. 3 Distribution of hyponatremia by the underlying mechanism. Pseudohypoaldosteronism includes congenital (mutations of the *NR3C2* gene) and secondary pseudohypoaldosteronism (pyelonephritis). Hypoaldosteronism is due to a mutation of the *CYP11B2* gene

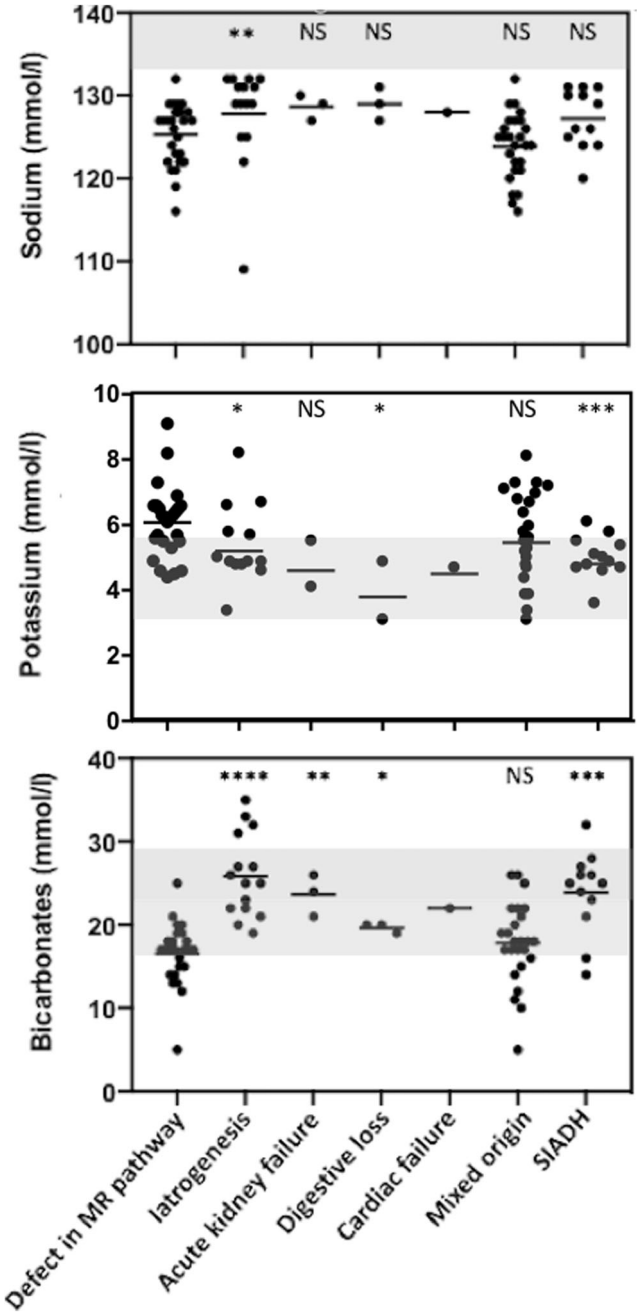

Fig. 4 Serum sodium, potassium, and bicarbonate concentrations, by the underlying mechanism of hyponatremia. Ion concentrations were compared with those in patients with mineralocorticoid pathway defects. MR, mineralocorticoid; NS, non-significant. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$. Gray rectangles indicate the normal range

during the postoperative period [4, 11] and a strict control of fluid intake is also recommended, to prevent iatrogenic hyponatremia. Diuretics are a major cause of hospital-acquired hyponatremia [31], and blood tests should be performed regularly to check for hyponatremia in patients on diuretic treatments. Physicians should pay particular attention when administering diuretic treatments in preterm neonates or critically ill children, because hyponatremia frequently has a mixed etiology.

Our findings confirmed the higher risk of death in children with hyponatremia [7]. Twelve patients (14.0%) died in our study, resulting in a mortality rate similar to that reported by Wattad et al. (12%) [31]. The reported deaths were not related to hyponatremia but were related to the severe underlying condition likely to have led to hyponatremia. Hyponatremia is not used as a risk factor in pediatric severity scores (e.g., IGSII, APACHE II), but it is used in the Score for Neonatal Acute Physiology-Perinatal Extension (SNAP-PE).

The prevalence of hyponatremia in this study was three times than that reported in the study by Wattad et al., which included a very large number of pediatric patients [31]. This difference may be explained by differences in the populations included in these two studies, as our study focused principally on neonatal hyponatremia and included preterm neonates. These findings highlight the higher risk of hyponatremia due to neonatal physiological renal salt-wasting in this fragile population.

Our findings shed new light on the pathophysiology of hyponatremia in young neonates. Several different etiologies were identified, and three patients from unrelated families (3.5%) were found to have an isolated constitutional defect of the mineralocorticoid signaling pathway (aldosterone synthase deficiency or mutations of the mineralocorticoid receptor gene), a frequency much higher than reported in other studies [1]. Type 1 pseudohypoaldosteronism and aldosynthase deficiency are extremely rare genetic diseases [25, 32]. The unexpectedly high prevalence of those abnormalities in our study suggests frequent underdiagnosis or overrepresentation in our patient population. In neonates with symptoms of pyelonephritis or severe gastro-enteritis presenting with hyponatremia and hyperkalemia, plasma hormone levels (renin, aldosterone, 17OHP, cortisol, and ACTH) should be evaluated to determine the cause of the ion disorders. If hyponatremia is profound and does not improve rapidly when sodium intake increases, or if it relapses, physicians should search for mutations of genes encoding proteins involved in the mineralocorticoid signaling pathway.

The mechanisms underlying hyponatremia are often poorly understood by or completely unknown to medical teams.

Hyponatremia may result from primary excess of ADH (SIADH), hypovolemia leading to ADH secretion or excessive hypotonic intravenous hydration. In order to prevent hyponatremia caused by excessive hypotonic IV fluids, enteral feeding should be preferred to IV fluids. However, if IV fluids are required, they should contain high levels of sodium (140 mmol/l) as previously demonstrated [21]. Hyponatremia often occurs in patients with severe clinical conditions in which those mechanisms may occur together, and electrolyte disorders are often left aside to focus on organ failure. However, once intensive care procedures have been initiated, doctors should try to correct hyponatremia to make sure that it

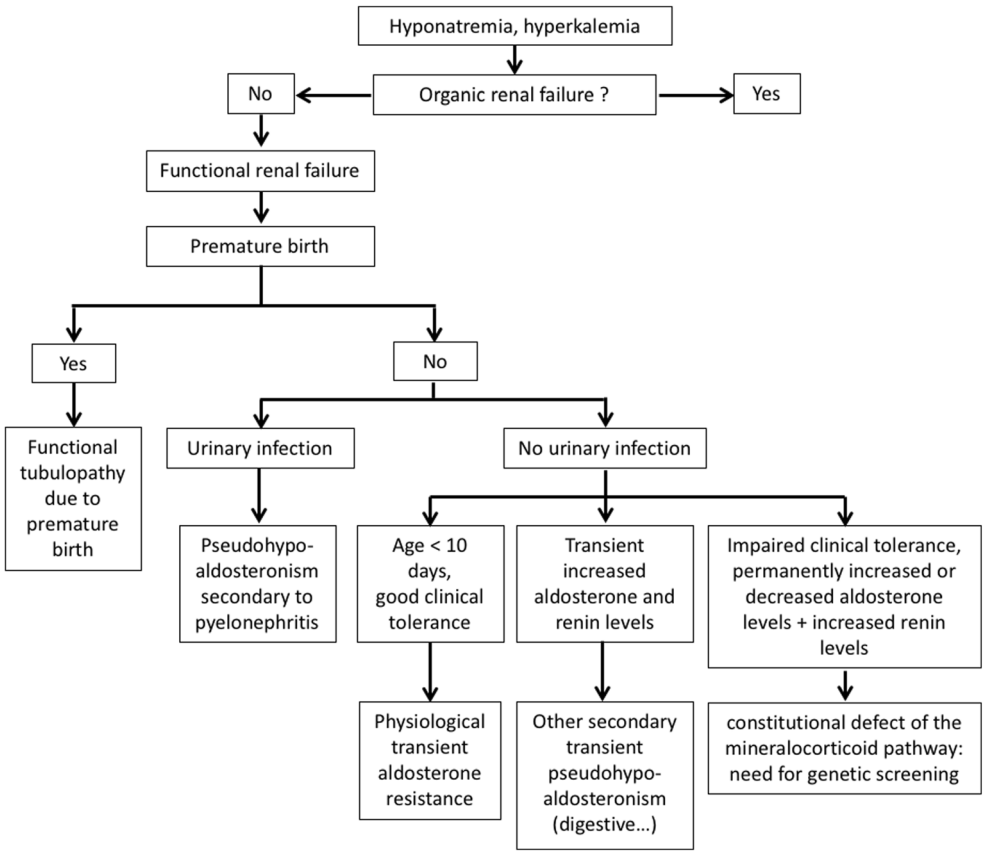

Fig. 5 Proposed diagnostic procedure for a neonate presenting with hyponatremia and hyperkalemia (suspected mineralocorticoid defect). Premature birth is defined as birth before 37 weeks of gestation, with a corrected gestational age of less than 37 weeks

does not worsen and to prevent morbidity due to electrolyte disorders. Serum bicarbonate concentration determinations can facilitate identification of the cause of hyponatremia, as these concentrations differ considerably between disease mechanisms. Identification of the underlying mechanism is crucial, because the most appropriate treatment differs between causes, particularly since the advent of new treatments, such as vaptans (non-peptide arginine-vasopressin-receptor antagonists), which can cure SIADH [16, 22] but may lead to adverse events if misused in patients with salt-wasting hyponatremia and extracellular dehydration. Finally, we propose a specific diagnostic diagram, to facilitate accurate diagnosis, as transient or permanent defects of the mineralocorticoid signaling pathway are frequently implicated in neonatal hyponatremia associated with hyperkalemia (Fig. 5).

Conclusion

Hyponatremia is a frequent electrolyte disorder in the neonatal population. Our findings indicate that it can be caused by various mechanisms, most of which could be avoided by optimized management. The most appropriate treatment depends entirely on the mechanism involved. Simplified diagrams to help pediatricians to investigate and manage hyponatremia are therefore crucial, to improve patient care.

Authors' Contributions Laetitia Martinerie designed the research.
Caroline Storey conducted the research and analyzed the data.
Caroline Storey, Laetitia Martinerie, and Jean-Claude Carel wrote the manuscript.
Stéphane Dauger, Georges Deschenes, Alice Heneau, and Olivier Baud contributed to data analysis and writing of the manuscript.
All of the authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement This retrospective observational study was reviewed and approved by the local ethical review committee for biomedical research (No. 2015/172) and the French data protection authority (CNIL No. 1827596), in accordance with the Declaration of Helsinki.

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