www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2023;12(2):e120207
doi: 10.7363/120207
Received: 2022 Mar 12; revised: 2022 Jul 08; rerevised: 2022 Jul 14; rerevised: 2022 Dec 01; accepted: 2022 Dec 14; published online: 2023 Oct 31

Review

Prevalence, risk factors, and prognosis of neonatal hypernatremic dehydration among full-term newborns: a systematic review

Maryam Zakerihamidi[1], Forough Rakhshanizadeh[2], Hassan Boskabadi[2]

[1]Department of Midwifery, School of Medical Sciences, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

[2]Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Introduction: Neonatal hypernatremic dehydration (NHD) is a major preventable problem associated with acute and chronic complications in neonates. Thus, the present study investigated the prevalence, risk factors, clinical signs, complications, and prognosis of NHD.

Materials and methods: In this study, we searched databases (PubMed, EMBASE and Google Scholar) for articles published until 2022. Keywords were: "hypernatremic dehydration", "neonatal", "risk factors", "prognosis", "complications", "prevalence", and "clinical signs". Persian- or English-language articles with sufficient data on NHD were included in the study. Finally, 24 relevant articles were examined.

Results: Significant weight loss, delayed first breastfeeding, breastfeeding frequency, early discharge, use of sugar water and manna, low frequency of urination and defecation, summer season, use of heaters, and late referral age are NHD risk factors. Jaundice, hyperthermia, lethargy, poor feeding, restlessness, decreased skin turgor, and seizure are the clinical signs of NHD. Laboratory findings include increased urea, creatinine, sugar, and sodium levels. Renal problems (azotemia, high creatinine, renal insufficiency, and stones), neurological complications (cerebral edema, seizure, loss of consciousness, cerebral hemorrhage, developmental delay, and hearing impairment), coagulopathy, and thrombocytopenia are the complications of NHD.

Conclusion: NHD and its complications could be prevented by prompt and appropriate prevention of risk factors, early detection based on clinical signs, and appropriate treatment.

Keywords

Neonatal hypernatremia dehydration, clinical signs, risk factors, neonatal, prognosis, complications.

Corresponding author

Hassan Boskabadi, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; email: boskabadih@mums.ac.ir.

How to cite

Zakerihamidi M, Rakhshanizadeh F, Boskabadi H. Prevalence, risk factors, and prognosis of neonatal hypernatremic dehydration among full-term newborns: a systematic review. J Pediatr Neonat Individual Med. 2023;12(2):e120207. doi: 10.7363/120207.

Introduction

Infants naturally experience weight loss of about 5-7% of their birth weight at 3-5 days of age, but it usually resolves by the end of the first week. If weight loss continues after 1 week of life or if weight loss is rapid (more than 2% of the infant's weight per day), it should be noted that the intake of milk and liquids is inadequate [1, 2].

In the case of breast milk intake reduction, as a defense mechanism, kidneys try to reabsorb urine sodium to maintain the body fluids, which results in hypernatremia. In addition, insensible water loss from the immature skin and lungs of these newborns continues, exacerbating dehydration [3]. In neonates, hypernatremia refers to serum sodium levels higher than 150 mmol/L [4]. Elevated sodium in breast milk is an important factor in neonatal hypernatremia [5]. Mechanisms of hypernatremia include: 1) water loss (renal, extra renal, or insensible water loss), 2) inadequate milk intake, and 3) excessive sodium intake [6].

Neonatal hypernatremic dehydration (NHD) caused by breastfeeding occurs in about 1-2% of hospitalized infants [1-39]. Due to increased serum osmolarity caused by hypernatremia [7], clinical signs of dehydration occur later in these newborns. Irritability, hyperthermia, jaundice, oliguria, weight loss, poor feeding, lethargy, mucosal dryness, seizure, loss of consciousness, and cyanosis [8] are clinical signs of NHD infants [9].

Laboratory data in favor of NHD include azotemia, hypernatremia, hypokalemia, hyperkalemia, and hyperbilirubinemia [10]. Complications of NHD include acute renal failure [11] and neurological complications (cerebral edema, cerebral hemorrhage, thrombosis, infarction, seizure, developmental delay, and hearing impairment) [8]. In a study, seizure was detected 15 times higher in hypernatremic neonates than in isonatremic neonates. Seizure occurrence may be associated with hypernatremia severity [12].

Considering the importance of NHD to neonatal outcomes, early detection and management of NHD risk factors can reduce neonatal complications and promote the newborns' health.

The present study systematically reviews the prevalence, risk factors, clinical signs, complications, and consequences of NHD.

Methods

Evaluation of risk factors and neonatal outcomes of hypernatremic dehydration

After a preliminary review of the searched articles, those that only examined NHD risk factors and its neonatal outcomes were studied. In this regard, articles containing prevalence, clinical signs, risk factors, complications, outcomes, and prognosis, or a combination of them, were included in the study.

Search strategy

PubMed, EMBASE, and Google Scholar databases were searched in this systematic review. We contacted study authors to identify additional studies. The search keywords included: "prevalence", "hypernatremic dehydration", "neonatal", "risk factors", "clinical signs", "complications", and "prognosis". Ninety-eight articles meeting the inclusion criteria were collected in a separate library file in the EndNote™ software. Two reviewers evaluated the initial articles and selected the papers found.

Of these papers, 25 duplicated articles were eliminated. The searched articles were evaluated in terms of title and abstract, and 35 were deleted at this stage. Among the remaining articles, 14 were omitted due to incomplete data, lack of full text, uncertainty of study type, and target group. Finally, 24 articles related to the research topic were studied (**Fig. 1**).

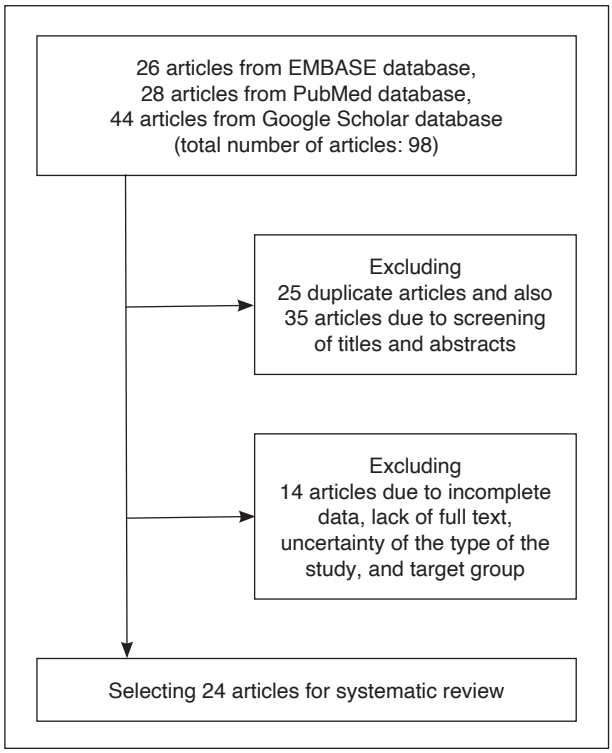

Figure 1. Search strategy and selected articles.

Inclusion criteria

1. Study population of infants,
2. confirmed NHD,
3. evaluation of neonatal risk factors for NHD,
4. assessment of neonatal complications and outcomes of NHD,
5. English- and Persian-language articles,
6. sufficient information on NHD status,
7. evaluation of the NHD prevalence,
8. evaluation of the NHD clinical signs,
9. assessment of predictive factors for NHD,
10. articles published until 2022, and
11. full-text articles.

Exclusion criteria

1. Case reports examining NHD,
2. studies whose target groups were not infants, and
3. articles where only the abstracts were available.

Data extraction and evaluation of articles' quality

Articles with full text were received from the aforementioned databases. The following data were extracted in Excel® software: authors' names and surnames, year of study, type of study, study location, case group, control group, prevalence, maternal risk factors, clinical signs, neonatal complications and outcomes of NHD, and research results. We determined the methodological quality of the articles using the tool for Quality Assessment of Diagnostic Accuracy Studies (QUADAS). This tool consists of 14 questions, for which "yes," "no," and "unspecified" options were scored 1, -1, and 0, respectively, giving a maximum score of 14 [13].

Results

Among 98 retrieved articles, finally, 24 articles with a sample size of 15,325 newborns were evaluated. Seven (29%) articles examined the prevalence of NHD, 14 (58%) assessed neonatal risk factors, 10 (42%) reviewed neonatal clinical symptoms and signs, 10 (42%) reviewed neonatal complications and outcomes, and 5 (21%) evaluated neonatal prognosis risk factors.

The abstracts of the articles are presented in **Tab. 1**.

Heterogeneity of studies

The searched studies were different regarding inclusion criteria, population, target group definition, research methodology, sample size, and location. Of them, 10 (42%) articles were cross-sectional studies, 3 (13%) were descriptive studies, 8 (34%) were prospective studies, 3 (13%) were retrospective studies (**Tab. 1**).

The worldwide distribution of studies associated with risk factors and neonatal outcomes of hypernatremia dehydration: 13 (54%) studies were from Iran, 4 (17%) from India, 4 (17%) from Turkey, 1 (4%) from the United States, 1 (4%) from Colombia, and 1 (4%) from Spain.

Prevalence

Based on the results of 7 studies, the incidence of NHD was reported to be 1.38% to 6.45% (**Tab. 1**).

Neonatal risk factors

A study in 2015 revealed that for daily weight loss of more than 1.5%, hypernatremia occurred with a sensitivity of 70%, specificity of 83.6%, positive predictive value of 50%, and negative predictive value of 92% [22]. Another study in 2014 showed a significant difference between the two groups of hypernatremic and isonatremic infants in

Table 1. Summary of studies on prevalence, risk factors, clinical symptoms and signs, complications and consequences, and prognosis of neonates with NHD (the table continues on the next page).

No.	Author/ year	Type of study	Location	Case and control group	Prevalence	Neonatal risk factors	Clinical symptoms and signs	Complications and consequences of NHD	Prognosis risk factors	Limitations and bias risks	QUADAS score
1	Boskabadi et al., 2015 [22]	Cross-sectional	Iran	273 neonates	-	Total weight loss of more than 7% or daily weight loss of more than 1.5%	-	-	-	Lack of a rigorous evaluation of pregnancy- and childbirth-related complications, accurate estimation of breast milk intake, and frequency of urination and bowel movements, No matching the age between case group and control group	13
2	Boskabadi et al., 2014 [23]	Cross-sectional	Iran	670 neonates	-	Weight on admission, type of feeding, frequency of breast-feeding, urination, and defecation	-	-	-	-	12
3	Boskabadi et al., [under publication] [38]	Cross-sectional	Iran	934 neonates	-	Age of infant, referral weight, frequency of nutrition, sodium, urea, creatinine, frequency of urination and defecation	-	-	-	-	11
4	Boskabadi et al., 2016 [1]	Descriptive-analytical	Iran	418 neonates	2.8%	First breast-feeding time and breast-feeding frequency	Jaundice (62.2%), hyperthermia (25.8%), lethargy (23.6%), restlessness (20.8%), mucosal dryness (17.2%), weight loss more than 10% (63%)	-	-	-	12
5	Uras et al., 2007 [2]	Retrospective	Turkey	1,150 neonates	3.7%	Weight loss of more than 7%, serum sodium, urea, creatinine, blood glucose	Jaundice (48%)	-	-	-	13
6	Boskabadi et al., 2014 [24]	Cross-sectional	Iran	273 neonates	-	Frequency of feeding, sucking problems, frequency of urination, first feeding time, weight loss severity	-	-	-	-	12
7	Boskabadi et al., 2010 [3]	Prospective	Iran	106 neonates	-	Weight loss, nutrition frequency	Fever, drowsiness, jaundice	-	-	-	13

Table 1. Summary of studies on prevalence, risk factors, clinical symptoms and signs, complications and consequences, and prognosis of neonates with NHD (the table continues from the previous page and on the next page).

No.	Author/ year	Type of study	Location	Case and control group	Prevalence	Neonatal risk factors	Clinical symptoms and signs	Complications and consequences of NHD	Prognosis risk factors	Limitations and bias risks	QUADAS score
8	Boskabadi et al., 2022 [39]	Cohort	Iran	183 neonates	-	-	-	-	High concentrations of sodium, urea, and creatinine; reduced urination, seizure, and decreased consciousness at the time of admission, and disruption of brain CT scan	-	13
9	Shah and Javadekar, 2018 [11]	Cross-sectional	India	434 neonates	6.45%	-	-	Renal dysfunction, sepsis, death	-	-	12
10	Boskabadi et al., 2014 [12]	Cross-sectional	Iran	110 neonates	-	-	-	Hearing impairment	-	-	12
11	Ahmed et al., 2014 [19]	Retro-spective	India	2,100 neonates	1.38%	Weight loss, lack of breast-feeding intake (72.41%), restlessness (68.96%), decreased urinary output (44.82%), jaundice (27.58%), fever (24.13%), and seizure (17.24%)	-	Coagulopathy (10.34%), hypoglycemia, hypokalemia, acute kidney injury (37.93%), and intraventricular hemorrhage	-	-	13
12	Boskabadi et al., 2017 [4]	Prospec-tive	Iran	130 neonates	-	Poor nutrition (61.5%), seizure (23.1%), hyperthermia (7.7%), restlessness (7.7%)	-	Developmental delay, cerebral edema, bleeding and kidney stones, growth retardation in the first year of birth	-	-	13
13	Boskabadi et al., 2020 [36]	Cohort	Iran	172 neonates	-	-	-	-	Hyperglycemia	-	11
14	Ergenekon et al., 2007 [20]	Descriptive and comp-arison with texts	Turkey	28 neonates	-	-	-	Developmental delay	-	-	13
15	Ramesh and Suvetha, 2017 [6]	Descriptive	India	201 neonates	-	Age of referral, weight loss percentage, serum sodium, summer season	Weight loss, jaundice, fever, dehydration	Acute renal injury, seizure, intracranial hemorrhage, apnea and bradycardia, neuro-developmental problems	-	Incomplete some data and lack of long-term formal neuro-developmental assessment	12
16	Caglar et al., 2006 [15]	Prospec-tive	Turkey	34 neonates with weight loss of 10% or more	-	Frequency of defecation less than 4 times per day, pink color diapers, delay in initiation of first breast-feeding, use of heaters	-	-	-	-	13

Table 1. Summary of studies on prevalence, risk factors, clinical symptoms and signs, complications and consequences, and prognosis of neonates with NHD (the table continues from the previous page and on the next page).

No.	Author/ year	Type of study	Location	Case and control group	Prevalence	Neonatal risk factors	Clinical symptoms and signs	Complications and consequences of NHD	Prognosis risk factors	Limitations and bias risks	QUADAS score
17	Boskabadi et al., 2022 [37]	Cohort with 36 months of follow-up	Iran	183 term newborns with NHD	-	-	-	82.5% normal and 17.5% with abnormal outcome (7% death and 10% developmental delay)	Combining the variables breast development, breastfeeding frequency, breastfeeding duration, seizure, decreased consciousness, urination frequency, urea, creatinine, and sodium, and brain CT scan. The combination of the aforementioned variables showed a high predictive value (98.6%)	-	12
18	Moritz et al., 2005 [8]	Retro-spective during a 5-year period	United States	3,718 term and near-term infants breastfed with levels of serum sodium 150 mmol/L	1.9% (70 neonates)	Primipara (87%), discharge within 48 hours after birth (90%)	The most common presenting symptom was jaundice (81%). The mean weight loss was 13.7%	Non-metabolic complications in 17% of infants, and the most common complication is apnea or bradycardia	Jaundice (81%), weight loss (13.7%)	-	12
19	Boskabadi et al., 2018 [21]	Cohort with 36 months of follow-up	Iran	390 neonates	-	Thrombo-cytopenia	Weight loss, increased serum urea, creatinine, sugar, and sodium	Cerebro-vascular complications and death	Thrombo-cytopenia	Not using more accurate paraclinical evaluations such as brain MRI and the other use of Denver Testing alone for assessing developmental delay	13
20	Nair et al., 2018 [9]	Cross-sectional	India	1,510 neonates	3.4%	-	Fever (34.6%), poor nutrition (42.8%), loose stool (40.8%), restlessness (26.5%), decreased urination (8.2%), weight loss (75.5%)	Neurological complications (24.5%), skin dryness (90%)	-	Its retrospective design, lack of neuro-development follow-up, lack of correlation between breast milk sodium levels and hypernatremia, and not recording correction rate in serum sodium levels in the first 6 and 24 hours	13
21	Borna et al., 2014 [10]	Cross-sectional	Iran	2,015 term neonates	5.2%	-	Drowsiness, fever, poor feeding, weight loss, orange urine, restlessness, seizure, decreased urine frequency, reduced skin turgor	-	-	-	12

Table 1. Summary of studies on prevalence, risk factors, clinical symptoms and signs, complications and consequences, and prognosis of neonates with NHD (the table continues from the previous page).

No.	Author/ year	Type of study	Location	Case and control group	Prevalence	Neonatal risk factors	Clinical symptoms and signs	Complications and consequences of NHD	Prognosis risk factors	Limitations and bias risks	QUADAS score
22	Akdeniz et al., 2021 [17]	Cross-sectional	Turkey	85 term neonates	-	-	Breastfeeding difficulties (90.5%), decreased urination (43.5%), fever (63.5%), jaundice (22.3%), convulsion (15.3%), metabolic acidosis (67%) and acute renal failure (74.4%)	-	-	-	12
23	Del Castillo et al., 2020 [18]	Cross-sectional	Colombia	43 term neonates	-	-	Breastfeeding problems (76.7%), weight loss (15.3%) and transient neurological signs (83.5%)	-	-	-	13
24	Ferrández-González et al., 2019 [16]	Prospec-tive	Spain	165 neonate more than 35 weeks	-	Weight loss (8.6%), male gender, higher education level, multiparity, and cesarean delivery	-	-	-	-	12

NHD: neonatal hypernatremic dehydration; QUADAS: Quality Assessment of Diagnostic Accuracy Studies.

terms of breastfeeding frequency, type of nutrition, and urination and defecation frequency [23]. In a study, there was a low frequency of feeding in 56% of newborns with hypernatremia, while 10% of isonatremic infants had this problem. Infants with frequent feeding of more than 8 times per day showed higher body weight, more urination and defecation frequency, and lower levels of sodium, urea, and creatinine [38].

In one study, in 2016, late first breastfeeding and less breastfeeding frequency were among hypernatremia risk factors in newborns [1]. In Uras et al.'s study, in 2007, 95% of hypernatremic neonates presented more than 7% weight loss, and there was a direct correlation between serum sodium and urea and creatinine levels. A reverse relationship was detected between serum sodium and glucose [2]. One study in 2013 reported that delayed initiation of first feeding, less frequent feeding, low urine frequency, and significant weight loss were risk factors for neonatal hypernatremia [14]. In another study, weight loss was observed in 1.6% of the control group and 16.2% of the case group. The feeding frequency in the control and case groups was 10.2 and 7.6 times daily, respectively [3]. In Ramesh and Suvetha's study, in 2017, there was a direct relationship between neonatal referral age, weight loss percentage, and serum sodium levels. The prevalence of hypernatremia was higher in the summer [6]. In the study by Caglar et al., in 2006, defecation frequency of fewer than 4 times a day, pink diapers, delayed first breastfeeding onset, and use of heaters were reported as risk factors. In this study, weight loss was significantly related to serum sodium and uric acid concentrations. Severe weight loss was detected in newborns with exclusive breastfeeding, which could be associated with hypernatremia and other complications [15]. NHD risk factors in Moritz et al.'s study, in 2005, included primipara (87%) and discharge within 48 hours after birth (90%) [8]. In the study by

Ferrández-González et al., in 2019, weight loss, male gender, higher education level, multiparity, and cesarean delivery were reported as risk factors [16].

Clinical symptoms and signs

In one study, in 2016, the most common clinical symptoms and signs of hypernatremic infants included severe weight loss (63%), jaundice (62.2%), hyperthermia (25.8%), lethargy (23.6%), restlessness (20.8%), and mucosa dryness (17.2%) [1]. In Uras et al.'s study in 2007, the most common symptom of NHD was jaundice (48%) [2]. In a study, the main manifestations of NHD were fever, drowsiness, and jaundice [3]. In another study, poor feeding (61.5%), seizure (23.1%), hyperthermia (7.7%), and restlessness (7.7%) were common signs of NHD [4]. In a study, weight loss, jaundice, hyperthermia, and dehydration were common signs [6].

In another study, the most common symptom of NHD was jaundice (81%). Also, neonates with moderate hypernatremia suffered 13.7% weight loss [8]. In Nair et al.'s study, in 2018, 49 (3.4%) out of 1,510 neonates referred to the Neonatal Intensive Care Unit (NICU) showed NHD. Hyperthermia (34.6%), poor nutrition (42.8%), loose stool (40.8%), restlessness (26.5%) and weight loss (75.5%) were common symptoms of NHD [9]. In the study by Borna et al., in 2014, the most common clinical symptoms of NHD were drowsiness, fever, poor feeding, and weight loss, which were observed in more than two-thirds of infants. Weight loss, orange urine, restlessness, seizure, decreased urine frequency, and reduced skin turgor were among the warning signs of hypernatremia, which had a significant relationship with hypernatremia severity [10]. In a study by Akdeniz et al., in 2021, the most common clinical symptoms of NHD were breastfeeding difficulties (90.5%), fever (63.5%), decreased urination (43.5%), jaundice (22.3%), convulsion (15.3%), metabolic acidosis (67%), and acute renal failure (74.4%) [17]. In the study of Del Castillo et al., in 2020, the most common clinical symptoms of NHD were breastfeeding problems (76.7%), weight loss (15.3%), and transient neurological signs (83.5%) [18].

Neonatal complications and outcomes

In a study, in 2018, of 434 newborns admitted to the NICU, 28 cases had dehydration, and 21 presented with hypernatremia. Almost all patients suffered from renal dysfunction at the time of admission and had normal conditions before discharge. Sepsis was proved in 4 patients based on blood cultures. Of 28 cases, 2 patients died, and 26 cases fully recovered [11]. In another study, 3 out of 110 NHD infants showed transient hearing impairment. This complication was observed in infants with severe hypernatremia [12]. In one study, in 2014, the complications of hypernatremia included seizure (17.24%), coagulopathy (10.34%), hypoglycemia, hypokalemia, acute renal injury (37.93%), and cerebral hemorrhage [19]. In one study, the prevalence of developmental delay in NHD infants was 25% at 6 months of age, 21% at 12 months, 19% at 18 months, and 12% at 24 months. Serious NHD complications were cerebral edema, hemorrhage, and renal stones [4].

Ergenekon et al., in 2007, evaluated NHD in term infants referred to the NICU. Two cases suffered from severe developmental delay. Five patients had moderate risk scores in the neurodevelopmental screening tests of Bayley [20]. Neonatal complications of NHD in Ramesh and Suvetha's study, in 2017, included acute renal injury, seizure, intracranial hemorrhage, apnea, bradycardia, and neurodevelopmental problems [6]. Neonatal complications of NHD were apnea and bradycardia in one study in 2005 [8] and neurological complications (24.5%) in another study in 2018 [9].

Neonatal hypernatremic dehydration prognosis predictors

In an article, the risk factors for abnormal outcomes in newborns with NHD included high levels of sodium, urea, and creatinine, inappropriate breastfeeding, decreased urination frequency, seizure, decreased levels of consciousness on referral, and impairment in brain CT scan [39]. In one study, thrombocytopenia was observed in 41% of patients with hypernatremia and 6% of isonatremic infants. In newborns with NHD, there was a strong correlation between hypernatremia and thrombocytopenia. In newborns with thrombocytopenia, more complications and worse prognosis were observed. NHD increased thrombocytopenia by 7-fold. NHD infants with thrombocytopenia had more cerebrovascular complications and higher mortality because they were referred late to the hospital and had greater

weight loss and higher serum urea, creatinine, sugar, and sodium levels [21]. The reason for the high incidence of thrombocytopenia among NHD infants is unknown [4, 21]. It is possibly because excessive peripheral consumption of platelets or severe hypernatremia has an inhibitory effect on the bone marrow's platelet production [21].

In a study that examined blood glucose in 172 NHD infants, 134 (77.91%) were normoglycemic, and 38 (22.09%) were hyperglycemic. Developmental delay cases were higher in the hyperglycemic NHD group. Among hyperglycemic NHD infants, referral age and sodium, urea, and creatinine levels were higher, while the referral weight, duration of breastfeeding, frequency of urination, and blood pH were lower than those in normoglycemic NHD infants. High serum glucose was reported to be a risk factor for poor prognosis in infants with NHD (prevalence of hyperglycemia and its relationship with the prognosis of neonates with NHD) [36]. Another study reviewed the prognosis of NHD in newborns. In the follow-up, 82.5% of infants showed normal conditions, and 17.5% showed abnormal outcomes. There was a significant difference between the two groups in terms of postpartum breast development, breastfeeding frequency, breastfeeding duration, seizure, decreased level of consciousness, urination frequency, serum levels of urea, creatinine, sodium, and brain CT scan findings. The combination of the aforementioned variables showed a high predictive value (98.6%) for determining poor prognosis in newborns with NHD [37].

Discussion

Based on the findings of this systematic review, the incidence of NHD was between 1.38% and 6.45% (**Tab. 1**).

In Iran, the prevalence of NHD is increasing, and parents, physicians, and healthcare staff are unaware of the importance of early detection, control, and treatment. The incidence of multiple complications in newborns with NHD, including developmental delay, suggests a need to review the care of newborns in the first weeks of life. Thus, early detection of risk factors for dehydration and the attention of parents and healthcare staff to the clinical symptoms in these infants may reduce the incidence or severity of dehydration complications [1].

Risk factors

In this review study, the risk factors for NHD included daily weight loss of more than 1.5%, significant weight loss (> 7%) and severe weight loss (> 10%), late first breastfeeding, frequency of breastfeeding fewer than 8 times per day, early discharge, use of sugar water and manna, reduced urination frequency, pink diapers, defecation frequency less than 4 times a day, summer season, use of warmers, and late admission age of infants (**Tab. 1**).

Attention to NHD's alarm signs, such as weight loss, decreased urine volume, jaundice, and restlessness, is essential, and especially a weight loss of more than 7% should not be considered normal in the first week of life. Obviously, attention to hypernatremic symptoms and measuring serum sodium levels in suspected cases can be effective in the early detection of hypernatremia and the reduction of its fatal complications [1].

The most common cause of weight loss and hypernatremia is inadequate breastfeeding [15]. In case of reduced breast milk intake, neonates' kidneys try to reabsorb urine sodium and maintain fluid as a defense mechanism, resulting in hypernatremia; in addition, the insensible water loss from the skin and lungs continues due to lack of adequate maturity, which can exacerbate dehydration. Consumption of sugar water and traditional products reduces breastfeeding, increases defecation frequency, and exacerbates weight loss. The aforementioned factors lead to abnormal weight loss, reduced urinary and fecal frequency, and restlessness in newborns. In one study, there was a significant relationship between neonatal hypernatremia and the frequency of breastfeeding [12]. The increased frequency of breastfeeding in the first days of life provides for the baby's needs; it also leads to an increase in breast milk volume and early milk outflow that can reduce the incidence of exacerbated weight loss and its complications [1].

Reduced milk intake can lead to weight loss, hypernatremia, and intensified jaundice. Since jaundice presentation peaks in the late first week of life, mothers' proper training in breastfeeding skills and continuous assessment of the neonate in terms of adequacy of milk intake in the first days of life may be effective in reducing jaundice and hypernatremia [3].

Delay in referral to the hospital seems to be an important risk factor for undesirable prognosis.

Probably, the late referral results in the exacerbation of hypernatremia and its complications and causes trouble in their rapid recovery [3]. In another study, neonates with NHD and thrombocytopenia had a late referral to the hospital [21]. Delayed referral of NHD infants causes intensified jaundice and renal failure. Hence, increasing the family's knowledge about the importance of weight loss and early referral may prevent renal failure and exacerbation of NHD complications [24].

Clinical symptoms and laboratory data

Severe weight loss, jaundice, hyperthermia, lethargy, poor feeding, restlessness, loose stool, orange urine, decreased urination frequency, decreased skin turgor, drowsiness, and seizure are significant clinical symptoms in NHD. Laboratory data include increased serum levels of urea, creatinine, sugar, and sodium (**Tab. 1**).

In one study, the most common clinical symptoms of NHD included lethargy, hyperthermia, poor feeding, and weight loss, and these symptoms were observed in more than two-thirds of infants [10]. The most common clinical symptoms of hypernatremic infants include jaundice, hyperthermia, lethargy, restlessness, and mucosal dryness [1]. A study showed a positive relationship between weight loss severity and hypernatremia severity. Therefore, the early identification of weight loss in infants can prevent significant weight loss and severe hypernatremia [8]. In a study in the Netherlands, a linear relationship was detected between the weight loss severity and serum sodium concentration, in which for every 10% increase in weight loss, serum sodium increased by 16 mEq/L [25].

It is recommended that serum sodium levels be controlled in icteric infants under the age of 10 days, with a total weight loss of more than 7% or a daily weight loss of more than 1.5% [26]. In a prospective study by Van Dommelen et al. [27], when relative changes in infant weight exceed a 2.5 standard deviation of 10% of birth weight, referral to the hospital was required 3 to 6 days after delivery. The sensitivity of this approach was 85.5%, with a specificity of 99.4%.

In some studies, the most common clinical manifestation of NHD was jaundice, which is due to inadequate breastfeeding [28, 29]. Hyperthermia is a common nonspecific symptom for admission of newborns to the Emergency Department, mainly due to dehydration [30]. In another study, the most common clinical findings of hypernatremia were drowsiness, hyperthermia, poor feeding, weight loss, and decreased urinary volume [10].

Complications

Renal problems (azotemia, high creatinine levels, renal failure, and renal stones), neurological complications (cerebral edema, seizure, disturbance of consciousness, intracerebral or intraventricular hemorrhage, cerebrovascular complications, developmental delay, and hearing impairment), coagulopathy, thrombocytopenia, hypoglycemia, apnea, and bradycardia are important complications of NHD (**Tab. 1**).

Severe NHD is associated with complications of cerebral edema, seizure, venous sinus thrombosis, intracranial hemorrhage, defuse intravascular coagulopathy, renal failure, permanent brain damage, and death [31]. Due to the rapid growth of infants in the first week of life, and the loss of a chance for colostrum intake on the first day of life, inadequate breastfeeding leads to NHD and neonatal complications [32].

Complications of NHD occur not only in the early stages of hypernatremia and loss of water but also following treatment and rehydration. Treatment of NHD is difficult because of the rapid drop in serum sodium concentration, even with careful intravascular fluid therapy. On the other hand, a quick reduction of sodium concentration during treatment is as dangerous as delayed or incomplete treatment and could result in cerebral edema, seizure, and neurological complications [33].

Renal failure can cause acid-base, fluid, and electrolyte disturbance, hypertension, and intracranial complications, hence increasing mortality and morbidity [28]. Serum sodium concentration above 158 mEq/L is associated with increased neonatal mortality [34]. In one study, 40% of newborns with NHD presented creatinine levels above 1 mg/dL [4]. In Ahmed et al. study in 2014 [19], there was a significant association between serum sodium concentration and acute renal injury. The serum sodium concentration and the chance of acute pre-renal injury increase with the advancement of dehydration. In addition, compared to normal renal function, patients with acute kidney injury experienced higher weight loss and were referred later to the hospital.

Prognosis

Risk factors for abnormal outcomes in infants with NHD included high concentrations of sodium, urea,

and creatinine, hyperglycemia, thrombocytopenia, acidosis, decreased urination frequency, seizure, reduced levels of consciousness at the time of referral, and abnormality in CT scan (**Tab. 1**). Likewise, a combination of the following variables, including seizure, decreased consciousness, urination frequency, urea, creatinine, sodium, and brain CT scans, are among the predictors of adverse effects of neonatal hypernatremia. In a study conducted in 2017, the main predictor signs and symptoms of adverse complications of neonates were poor feeding, seizure, hyperthermia, and agitation [4].

Kamrani et al. [35], in 2017, revealed that seizure in newborns with hypernatremia was associated with increased developmental problems in neonates. Ergenekon et al. [20], in 2007, described that high serum sodium levels during admission of hypernatremic neonates were associated with adverse effects of neurodevelopmental disorders. Early diagnosis and proper treatment can help improve infants' prognosis and survival. This critical issue would apply to educating mothers about the signs and symptoms of NHD after delivery and before discharge from the hospital [11].

Strengths and limitations of this study

One of the strengths of the present study is that, to our knowledge, the current study was the only systematic review of prevalence, risk factors, clinical symptoms and signs, complications, and prognosis of NHD in neonates.

The limitations of the present study include the lack of access to all papers and unpublished reports, lack of proper, high-quality, and applicable reports, lack of clear and identical reports in the studies of NHD, and lack of identical definitions for the case group in studies.

Conclusion

The incidence of NHD is between 1% and 6%.

Important risk factors for NHD include significant daily weight loss, later time of first breastfeeding, the frequency of breastfeeding less than 8 times per day, early discharge, the use of water glucose and manna, urination frequency less than normal, pink diapers, defecation frequency less than 4 times per a day, summer season, use of warmers, and the later age of referral of infants.

Severe weight loss, jaundice, hyperthermia, lethargy, poor feeding, restlessness, drowsiness, loose stool, orange urine, decreased urination frequency, reduced skin turgor, and seizure are important clinical symptoms of NHD.

Renal problems, neurological complications, coagulopathy, thrombocytopenia, hypoglycemia, apnea, and bradycardia were the most important complications of NHD.

Risk factors for the abnormal outcome of newborns with NHD include high concentrations of sodium, urea, and creatinine, hyperglycemia, thrombocytopenia, acidosis, decreased urination frequency, seizure, reduced consciousness at the time of referral, and abnormality in brain CT scan.

Systematic review registration

Systematic review registration number: 970869, IR.MUMS.MEDICAL.REC.1398.143.

Declaration of interest

The Authors declare that there is no conflict of interest. Funding: not applicable.

References

1. Boskabadi H, Kalateh Molaee M. Survey of Clinical Evidence in Newborns with Hypernatremic Dehydration. J Ardabil Univ Med Sci. 2016;15(4):441-50.
2. Uras N, Karadag A, Dogan G, Tonbul A, Tatli MM. Moderate hypernatremic dehydration in newborn infants: retrospective evaluation of 64 cases. J Matern Fetal Neonat Med. 2007;20(6):449-52.
3. Boskabadi H, Maamouri G, Ebrahimi M, Ghayour-Mobarhan M, Esmaeily H, Sahebkar A, Ferns GA. Neonatal hypernatremia and dehydration in infants receiving inadequate breastfeeding. Asia Pac J Clin Nutr. 2010;19(3):301-7.
4. Boskabadi H, Akhondian J, Afarideh M, Maamouri G, Bagheri S, Parizadeh SM, Mobarhan MG, Mohammadi S, Frens GA. Long-term neurodevelopmental outcome of neonates with hypernatremic dehydration. Breastfeeding Med. 2017;12(3):163-8.
5. Mujawar NS, Jaiswal AN. Hypernatremia in the neonate: Neonatal hypernatremia and hypernatremic dehydration in neonates receiving exclusive breastfeeding. Indian J Crit Care Med. 2017;21(1):30.
6. Ramesh S, Suvetha K. Predisposing factors and outcome of hypernatremia in breastfed late preterm and term neonates. Indian J Child Health. 2017;4(4):561-5.
7. Vadi S, Yim K. Hypernatremia due to urea-induced osmotic diuresis: Physiology at the bedside. Indian J Crit Care Med. 2018;22(9):664.
8. Moritz ML, Manole MD, Bogen DL, Ayus JC. Breastfeeding-associated hypernatremia: are we missing the diagnosis? Pediatrics. 2005;116(3):e343-e7.

9. Nair S, Singh A, Jajoo M. Clinical Profile of Neonates with Hypernatremic Dehydration in an Outborn Neonatal Intensive Care Unit. Indian Pediatr. 2018;55(4):301-5.
10. Borna H, Rafati S, Haj Ebrahim Tehrani F. The frequency of clinical and laboratory findings of hypernatremia and factors affecting its severity in term newborns. Tehran Univ Med J. 2014;72(8): 546-54.
11. Shah RH, Javadekar BB. Clinical profile and outcome of neonates admitted during summer months with dehydration and hypernatremia in tertiary care hospital of central Gujarat, India. Int J Contemp Pediatr. 2018;5(3):761-3.
12. Boskabadi H, Anvarifar F, Nourizadeh N. Could neonatal hypernatremia dehydration influence hearing status? Iran J Otorhinolaryngol. 2014;26(74):13.
13. Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. BMC Med Res Methodol. 2006;6(1):1-8.
14. Boskabadi H, Abdollahy A, Maamouri G, Esmaeili H. Factors associated with hypernatremia in term infants with jaundice. Iran J Obstet Gynecol Infertil. 2013;16(63):1-7.
15. Caglar M, Özer I, Altugan F. Risk factors for excess weight loss and hypernatremia in exclusively breast-fed infants. Braz J Med Biol Res. 2006;39(4):539-44.
16. Ferrández-González M, Bosch-Giménez V, López-Lozano J, Moreno-López N, Palazón-Bru A, Cortés-Castell E. Weight loss thresholds to detect early hypernatremia in newborns. J Pediatr. 2019;95:689-95.
17. Akdeniz O, Çelik M, Samancı S. Evaluation of Term Newborn Patients With Hypernatremic Dehydration. Turk Arch Pediatr. 2021;56(4):344.
18. Del Castillo C, Suares A, Granja A, Oviedo E, Urbano U, Cabrera B. Characterization of full term newborns with hypernatremic dehydration. Rev Chil Pediatr. 2020;91(6):874-80.
19. Ahmed A, Iqbal J, Ahmad I, Charoo BA, Ahmad QI, Ahmad SM. Complications due to breastfeeding associated hypernatremic dehydration. J Clin Neonatol. 2014;3(3):153.
20. Ergenekon E, Unal S, Gücüyener K, Soysal SE, Koç E, Okumus N, Türkyilmaz C, Onal E, Atalay Y. Hypernatremic dehydration in the newborn period and long-term follow up. Pediatr Int. 2007;49(1):19-23.
21. Boskabadi H, Rakhshanizadeh F. Neonatal Hypernatremic Dehydration and Thrombocytopenia: Its Prevalence and Relationship with Prognosis. Iran J Pediatr. 2018;28(4):e65742.
22. Boskabadi H, Maamouri G, Khatami F, Kiani MA, Abdollahi A, Zakerhamidi M, Saghafi N, Ghazizadeh Hashemi A. Evaluation of the sodium serum level in infants with Jaundice. Int J Pediatr. 2015;3(3.1):609-17.
23. Boskabadi H, Godarzi M, Zakerihamidi M. The study of the relationship between hypernatremia in neonates and mode of maternal breast feeding in hospitalized infants in Ghaem Hospital of Mashhad, Iran. Iran J Obstet Gynecol Infertil. 2014;16(90): 1-9.
24. Boskabadi H, Maamouri G, Bagheri S. Significant neonatal weight loss related to idiopathic neonatal hyperbilirubinemia. Int J Pediatr. 2014;2(4.1):225-31.
25. Breuning-Boers JM, van Dommelen P, van Wouwe JP, Verkerk PH. [Weight loss, serum sodium concentration and residual symptoms in patients with hypernatremic dehydration caused by insufficient breastfeeding]. [Article in Dutch]. Ned Tijdschr Geneeskd. 2006;150(16):904-8.
26. Boskabadi H, Maamouri G, Mafinejad S. The effect of traditional remedies (Camel's Thorn, Flixweed and Sugar Water) on idiopathic neonatal jaundice. Iran J Pediatr. 2011;21(3):325.
27. van Dommelen P, van Wouwe JP, Breuning-Boers JM, van Buuren S, Verkerk PH. Reference chart for relative weight change to detect hypernatraemic dehydration. Arch Dis Child. 2007;92(6):490-4.
28. Unal S, Arhan E, Kara N, Uncu N, Aliefendioğlu D. Breast-feeding-associated hypernatremia: Retrospective analysis of 169 term newborns. Pediatr Int. 2008;50(1):29-34.
29. Kamrani K, Sanaei Z, Khosroshahi N, Eslami SR, Amiri J. Hypernatremic Dehydration in Term and Preterm Neonates. Sci J Hamadan Univ Med Sci. 2015;22(3):203-9.
30. Coates B, Camarda L, Goodman D, Kliegman R, Stanton B, Geme JS. Nelson textbook of pediatrics. Philadelphia: Elsevier, 2016.
31. Modi N. Avoiding hypernatraemic dehydration in healthy term infants. Arch Dis Child. 2007;92(6):474-5.
32. Leung AK, Sauve RS. Breast is best for babies. J Natl Med Assoc. 2005;97(7):1010.
33. Abdelaziz E, Petrik N. Hypernatremic dehydration in infancy. Sudanese J Paediatr. 2007;8:161-70.
34. Özdogan T, Iscan M, Ellikcioglu C, Yildiz E. Hypernatraemic dehydration in breast-fed neonates. Arch Dis Child. 2006;91(12):1041.
35. Kamrani K, Amiri J, Khosroshahi N. Risk factors and neurological outcomes of neonatal hypernatremia. Iran J Neonatol. 2017;8(3):38-43.
36. Boskabadi H, Zakerihamidi M. The prevalence of hyperglycemia in neonatal hypernatremic dehydration (NHD) and its correlation with prognosis in exclusively breastfed infants: A cohort study. Acta Pediatr Mex. 2020;41(6):249-56.
37. Boskabadi H, Zakerihamidi M, Moradi A. Predictability of prognosis of infantile hypernatremic dehydration: a prospective cohort study. J Matern Fetal Neonatal Med. 2022;35(1):66-74.
38. Boskabadi H, Moradi A, Ramazani A, Zakerihamidi M. The Relationship between Breastfeeding Frequency and Neonatal Dehydration Hypernatremia. Clinical Lactation. [Under Publication].
39. Boskabadi H, Zakerihamidi M, Moradi A. Predictability of prognosis of infantile hypernatremic dehydration: a prospective cohort study. J Matern Fetal Neonatal Med. 2022;35(1):66-74.