J Pediatr Res 2020;7(2):139-45
DOI: 10.4274/jpr.galenos.2019.46547

Original Article

Hyponatremia in Children with Acute Lymphoblastic Leukemia

Deniz Yılmaz Karapınar[1], Akkız Şahin[1], Selime Özen[2], Pınar Yazıcı Özkaya[3], Zühal Önder Siviş[1], Ayşe Burcu Akıncı[1], Nihal Özdemir Karadaş[1], Bülent Karapınar[3]

[1]Ege University Faculty of Medicine, Department of Pediatric Hematology, İzmir, Turkey
[2]Ege University Faculty of Medicine, Department of Pediatrics, İzmir, Turkey
[3]Ege University Faculty of Medicine, Department of Pediatric Critical Care, İzmir, Turkey

ABSTRACT

Aim: Hyponatremia is a common electrolyte abnormality in hospitalized patients. Administration of isotonic maintenance fluids is recommended to prevent hyponatremia. The present study was conducted to evaluate the frequency and severity of hyponatremia in children with acute lymphoblastic leukemia (ALL).

Materials and Methods: The frequency, severity and possible causes of hyponatremia in children with ALL throughout their entire intensive treatment were retrospectively evaluated. All children in this study received isotonic fluids as maintenance IV treatment during the hospitalization period.

Results: In a five-year period, 618 hyponatremia episodes seen in 92 children with ALL (median age 59 months), treated with ALLIC 2002 protocol were entered into the study. The median number of hyponatremia episodes per patient was 6. All patients had at least one hyponatremia episode of which 83.2% were classified as mild, 13.2% as moderate, 2.9% as severe and 0.6% as very severe. The median duration of hyponatremia episodes was 5 (range between 1-43) days. The total duration of all hyponatremia episodes of each patient varied from 6 to 138 days with a median of 30 days. In 241 episodes of 68 children, there was inadequate salt intake secondary to oral feeding intolerance, nausea, vomiting and oral aphthous stomatitis. In four patients, seizure was seen during the hyponatremia period and thought to be secondary to hyponatremic encephalopathy. No patient developed central pontine myelinolysis.

Conclusion: Hyponatremia is very frequent in ALL patients. Despite the use of isotonic IV fluids, it seems it cannot be completely prevented.

Keywords: Hyponatremia, children, acute lymphoblastic leukemia, isotonic fluid

Introduction

Hyponatremia is the most common electrolyte abnormality encountered in children and occurs in almost 25% of hospitalized children and typically results from the combination of arginine vasopressin (AVP) excess plus free water intake (1-3). Intravenous hypotonic fluid administration has been identified as a major risk factor for hospital-acquired hyponatremia, therefore, many recommend the use of isotonic IV fluid, such as 0.9% NaCl (4-8). Even non-symptomatic hyponatremia can cause some neurological sequelae (9-12). It is necessary to promptly identify, and more importantly, to prevent hospital acquired

Address for Correspondence
Deniz Yılmaz Karapınar MD, Ege University Faculty of Medicine, Department of Pediatric Hematology, İzmir, Turkey
Phone: + 90 232 390 11 13 E-mail: dyilmazk@yahoo.com ORCID: orcid.org/0000-0002-1637-4678
Received: *19.03.2019* **Accepted:** *13.08.2019*

hyponatremia to minimize the patients' mortality and morbidity. In cancer and leukemia patients, hyponatremia is frequent and can cause severe issues (5,6,13-16).

In this study, we aimed to determine the frequency of hyponatremia and the riskiest periods during intensive chemotherapy in children with acute lymphoblastic leukemia (ALL).

Materials and Methods

This retrospective study was conducted at Ege University Faculty of Medicine, Children's Hospital, a tertiary care pediatric university hospital. All patients with a diagnosis of ALL treated with the protocol of ALLIC 2002 at this institution between February 2007 to 2012 were included in the study. These patients received intravenous isotonic maintenance fluid when they required intravenous fluid during their hospitalization period. Patients' charts were reviewed to detect if the patients had hyponatremia or not from the initial diagnosis to the initiation of maintenance therapy. If the patient had hyponatremia, the duration of the hyponatremia episodes, the lowest Na levels during each episode, the timing of the episodes, and the approach and treatment of hyponatremia were recorded.

The Glomerular filtration rate was calculated using the Schwartz equation.

Hyponatremia was defined as serum Na level <135 mEq/L. The severity of hyponatremia was defined as follows: Mild hyponatremia: Na level between 130-134 mEq/L, moderate hyponatremia: Na level between 125-129 mEq/L, severe hyponatremia: Na level between 120-124 mEq/L and very severe hyponatremia: Na level below 120 mEq/L.

ALL Treatment Protocol

Protocol I Phase I: It lasts for 33 days. For the first 7 days, patients receive only steroid and the dose starts from 15 mg/m^2/day and increases gradually. After the 8th day of initiation, they receive 60mg/m^2 prednisolon daily, vincristine (1.5 mg/m^2) weekly for 4 weeks (at day 8,15,22 and 29), daunorubicine (30mg/m^2/day) weekly for 2 weeks for patients in SRG (at day 8 and 15), 4 times for the others (at day 8,15,22 and 29). L-Asparaginase (5.000 U/m^2/day) on 8 occasions (at day 12, 15, 18, 21, 24, 27, 30 and 33).

Protocol I Phase II: It starts at day 36 and lasts for 28 days. The patients receive cyclophosphamide (1.000 mg/m^2/day) at day 36 and 64. Patient receive 6 mercaptopurine 60 mg/m^2/day P.O. on days 36 to 63, a total of 28 days and cytarabine (75 mg/m^2/day) in 4 blocks over 4 days each, on days 38 to 41, 45 to 48, 52 to 55, and 59 to 62.

Protocol M: It begins 2 weeks following the end of Protocol I Phase II for patients in SRG or MRG. Patients receive 6 mercaptopurine 25 mg/m^2/day P.O. on days 1-56. Methotrexate 2 g/m^2/day every 2 weeks 4 times. Patients receive intravenous hydration, 12 hours before to 72 hours after initiation of methotrexate infusion**.** Patients were hospitalized every 15 days for 3-4 days.

Protocol II Phase I: This protocol begins 2 weeks after the completion of Protocol M for SRG and MRG patients or the last high risk (HR) Blocks for HRG patients. In this protocol dexamethasone 10 mg/m^2/day is given on days 1-21. Then, the dose is tapered and the last dose is given on day 30. Vincristine (1.5 mg/m^2) weekly on 4 occasions (on day 8, 15, 22 and 29), doxorubicine (30 mg/m^2/day) weekly on 4 occasions (on day 8, 15, 22 and 29). ***L***-Asparaginase (10,000 U/m^2/day) on 8 occasions (on day 8, 11, 15 and 18). Patients mostly were seen at the outpatient service.

Protocol II Phase II: It starts on day 36 and lasts for 14 days. The patients receive cyclophosphamide (1,000 mg/m^2/day) on day 36. Intravenous hydration is made with 3,000 mL/m^2/day for diuresis and cystitis prophylaxis. Patient receive 6 tioguanine 60 mg/m^2/day P.O. on days 36 to 49, a total of 14 days and cytarabine (75 mg/m^2/day) in 2 blocks over 4 days each, on days 38 to 41 and days 45 to 48.

Block HR I: All HR patients receive 3,000 mL/m^2/day from the beginning of the block to the end of the block. Dexametasone P.O. or IV 20 mg/m^2/day on days 1 to 5; vincristine IV 1.5 mg/m^2/day on days 1 to 6; high dose methotrexate 5 g/m^2/day over 24 hours on day 1; cyclophosphamide 200 mg/m^2/day on days 2 to 4.5 doses every 12 hours apart, beginning 7 hours after the end of high dose methotrexate; high dose cytarabine 2 g/m^2/dose on day 5, two doses 12 hours apart; L-Asparaginase 25,000 U/m^2 on day 6.

Block HR II: All HR patients receive 3,000 mL/m^2/day from the beginning of the block to the end of the block. Dexametasone P.O. or IV 20 mg/m^2/day on days 1 to 5; vincristine IV 1.5 mg/m^2/day on days 1 to 6; high dose methotrexate 5 g/m^2/day over 24 hours on day 1; ifosfamide 800 mg/m^2/day on days 2 to 4,5 doses every 12 hours apart, beginning 7 hours after the end of high dose methotrexate; daunorubicin 30/m^2 on day 5, *E.Coli* L-Asparaginase ***25***,000 U/m^2 on day 6.

Block HR III: Dexametasone P.O. or IV 20 mg/m^2/day on days 1 to 5; high dose cytarabine 2 g/m^2/dose on days 1 and 2, 4 doses 12 hours apart; etoposide 100 mg/m^2/day on days 3 to 5, 5 doses, 12 hours apart; L-Asparaginase 25,000 U/m^2 on day 6.

Results

Characteristics of the Patients

In a five year period, 92 ALL patients were treated at the Pediatric Hematology Department of this tertiary care university hospital. All patients received isotonic intravenous maintenance fluid during the hospitalization period if they required intravenous fluid. If the patients had no hypertension, diabetes mellitus or any type of metabolic disease, they received a regular diet without salt restriction. The median age of the study population was 59 months (range 12 months to 18 years) with a male to female ratio of 1.36. Thirty eight percent of the patients (n=35) were categorized as HR, 35.9% (n=33) of them were categorized as median risk (MR) and the remaining 26% (n=24) as standard risk (SR) groups. They received the appropriate chemotherapy protocols according to their risk groups. Two patients (one in MR and one in SR) died at the end of protocol 1, eight patients in the HR group underwent bone marrow transplantation (BMT) after four HR blocks. Therefore, 90 out of 92 patients received protocol 1 phase 2, 55 out of 57 patients with SR or MR received protocol M, and 82 out of 92 patients received protocol 2 treatment.

Thirty three out of 90 patients were on voriconazol treatment, 22 patients were receiving ambisome and 17 patients were on combined antifungal therapy when they developed hyponatremia.

Severity of Hyponatremia

A total of 618 hyponatremia episodes were seen in 92 patients during the study period. The median number of hyponatremia episodes per patient was 6 (range between 1 and 25) during the period from the initial diagnosis to the end of intense chemotherapy protocol for ALL (cessation of treatment before initiation of maintenance treatment or BMT or patient death, of which one occurred before). All patients had at least one hyponatremia episode. Among these episodes, 83.2% (n=514) were classified as mild, 13.2% (n=82) moderate, 2.9% (n=18) severe and 0.6% (n=4) very severe hyponatremia.

Eighty-eight patients (95.6%) had at least one episode of mild hyponatremia, 49 (53.3%) had at least one episode of moderate hyponatremia, 15 (16.3%) had at least one severe and 4 (4.4%) patients had at least one very severe hyponatremia episode.

Duration and Timing of Hyponatremia Episodes

The median duration of hyponatremia episodes was 5 (range between 1 to 43) days. The median of the lowest Na levels of patients during all episodes was 125 (range from 110 to 133.9) mEq/L. The total duration of all hyponatremia episodes of patients varied from 6 to 138 days with a median of 30 days. In 92 episodes, the duration of hyponatremia was longer than 10 days.

Ninety out of 92 patients (97.8%) had at least one hyponatremia episode during protocol I phase I. The percentage of patients who had at least one hyponatremia during the treatment phases were 64.6% (n=53 out of 82 patients) at protocol II phase I, 60% (n=54 out of 90 patients) at protocol I phase II, 58.2 % (n= 32 out of 55 patients) at protocol M. The lowest number was seen at protocol II phase II with a rate of 23.2% (n=19 out of 82 patients).

Hyponatremia was seen at a rate of 54.3% (n=19 out of 35 patients) among HR patients during the period of 6 HR blocks.

Laboratory Investigation and the Causes of Hyponatremia

In 241 (38.9%) episodes of 68 children, oral feeding intolerance during the hyponatremia period occurred. Nausea, vomiting and oral aphthous stomatitis were the major causes of feeding intolerance.

The Glomerular filtration rate was checked in 243 out of 618 episodes (39.3%) and found to be normal for age in all. Plasma osmolality was checked in 315 hyponatremia episodes (50.9%) of 79 patients. It was low in 279 episodes (88.6% of the tested episodes) in 67 patients. High plasma osmolality was detected in 12 episodes (3.8% of tested episodes) of 7 patients. Tubular phosphate reabsorption was checked in 38 (41.3%) patients in 46 (7.4%) different episodes. It was found to be decreased (below 75%) in 24 (52.2% of tested episodes) hyponatremia episodes in 17 patients.

Urine osmolality was checked in 78 (84.7%) patients in 374 (60.5%) hyponatremia episodes.

Urine Na level was checked in 135 (21.8%) episodes of 62 (67.4%) different patients. It was below 20 mmol/L in 38 patients in 65 episodes (48.1% of tested episodes) and above 20 mmol/L in 51 patients in 70 episodes (51.8% of tested episodes)

Renal salt loss was seen in 56 episodes (9% of all episodes) of 41 patients. Renal tubular dysfunction (in 47 episodes of 33 patients) and diuretic therapy (in 9 episodes of 8 patients) were the most commonly seen causes or contributing factors of renal salt-wasting.

In 57 (9.2 %) episodes of 34 children, extrarenal loss of Na in excess water was seen (diarrhea in 41 (71.9%) episodes

of 23 children and third space loss in 9 (15.8%) episodes of 6 children, and both in 7 (12.3%) episodes and 5 patients).

In 32 (5.1%) episodes of 11 (12%) children, hyperglycemia was seen. In twelve of these episodes, hyperglycemia was the only factor that could have caused hyponatremia. Plasma osmolality was found to be high and hyponatremia was classified as factitious hyponatremia in 12 episodes (1.9%) of 7 children. In 4 episodes of 2 children, hyperlipidemia with hypertriglyceridemia was detected while plasma osmolality was normal and the osmolal gap was higher than 10 mosm/kg. These episodes were classified as pseudohyponatremia.

Renal loss of salt was seen in 56 (9.1%) episodes of 41 patients. Renal tubular dysfunction (in 47 episodes of 33 patients) and diuretic therapy (in 9 episodes of 8 patients) were the most commonly seen causes or contributing factors of renal salt-wasting.

SIADH was defined in 14 (2.3%) episodes of 12 patients. Eleven of these episodes were seen while the patients were receiving Protocol 1 Phase1, after 3rd or 4th vincristine treatment, 3 of these occurred during Protocol 2 Phase 1.

Seven out of 12 patients with SIADH were also on voriconazol treatment.

In 241 episodes of 68 children, there was inadequate salt intake secondary to oral feeding intolerance, nausea, vomiting, corticosteroid therapy, and oral aphthous stomatitis.

Clinical Symptoms of Hyponatremia

Headache, nausea, vomiting, lethargy, weakness and agitation were the most frequently seen symptoms in patients with hyponatremia. However, these symptoms were not attributed to hyponatremia by physicians. Headache was seen 7% of all episodes (43 out of 618 episodes) and 63.6% of severe and very severe hyponatremia episodes (14 out of 22 episodes). In all episodes, serum Na was below 127 mEq/L. In 32 episodes, patients also had anemia below 9 g/dL and in 14 episodes, patients had received intrathecal treatment beforehand. Anemia was considered as the cause of the headache and red blood cell transfusion was given to patients in 25 episodes. In patients who had intrathecal treatment before were given analgesic treatment. In two patients with severe hyponatremia, it was considered as a sign of hyponatremic encephalopathy.

In four patients, seizure was seen during the hyponatremia period and thought to be secondary to hyponatremic encephalopathy. No patient developed central pontine myelinolysis.

Treatment

Mild or moderate hyponatremia was not treated in 328 episodes (66.1%). When treatment was given in cases of mild or moderate hyponatremia, it was made with an increment of Na amount 1-10 mEq/L in the parenteral solution if patients were receiving parenteral fluid in 82 episodes (13.7%), or by adding more Na into the oral diet in 186 episodes (31.2%).

In 12 patients with a diagnosis of SIADH, fluid intake was restricted to 1,200 cc/m^2.

Characteristics of the Patients with Severe and Very Severe Hyponatremia

Eighteen severe and very severe hyponatremia episodes were seen in 14 patients (5 girls and 9 boys). The median age of the patients was 11 years and 7 months (range: 31 months to 15 years and 8 months). Eight of them were treated in the HR group, 3 in MR and the remaining 3 was in the SR group.

In 10 patients, only one severe hyponatremia episode was seen and 4 patients experienced 2 different severe hyponatremia episodes. The median duration of severe or very severe hyponatremia episodes was 26 (range; 8 to 36) days. Eleven of those episodes (61.1%) were seen in protocol II phase I, 4 (22.2%) of them in protocol I phase I, two (11.1%) in protocol I phase II and the other one (5.6%) in protocol II phase II. This is shown in Table I.

In protocol 2 phase 1, 12.2% of the hyponatremia episodes (n=11 out of 90) were severe or very severe hyponatremia. This rate was found to be 3.6% in protocol II phase II and only 1.7% (n=4 out of 227) in protocol I phase I and 1.75% (1 out of 28 episodes) in protocol I phase II. During the protocol M and HR blocks, no severe or very severe hyponatremia episodes occurred. This is shown in Table I.

Seven out of 11 patients with severe hyponatremia were receiving voriconazole treatment. The remaining 4 patients were not on anti-fungal therapy when they developed severe hyponatremia.

Nine patients in 10 different episodes had fever when severe or very severe hyponatremia was detected. In two of these episodes, sepsis was seen in two patients. Diarrhea, oral mucositis, feeding intolerance or severe abdominal pain were seen in 6 episodes of 6 patients. Dehydration was seen in 4 episodes of these 4 patients. Table II and Figure 1 summarizes the frequencies of mild, moderate, severe and very severe hyponatremia episodes in the different stages of the treatment protocol.

Hyperglycemia was detected in 4 episodes of 3 patients, all were seen during protocol II phase I. This rate was significantly higher than that of patients with mild or moderate hyponatremia (Table II). No additional risk factor for hyponatremia was detected in 3 episodes of 2 patients.

Six patients who were treated with hypertonic saline solution due to hyponatremic encephalopathy had severe

or very severe hyponatremia. After administration of 3% NaCl at a dose of 2 cc/kg over 10 minutes, serum Na level increased 3-6 mEq/L and the symptoms and physical findings attributed to hyponatremia resolved in ten of them. In two patients, encephalopathy resolved after a second administration.

No patient showed noncardiogenic pulmonary edema, central pontine or extrapontine myelinolysis. No patient who entered into the study showed neurological sequelae or death due to hyponatremia.

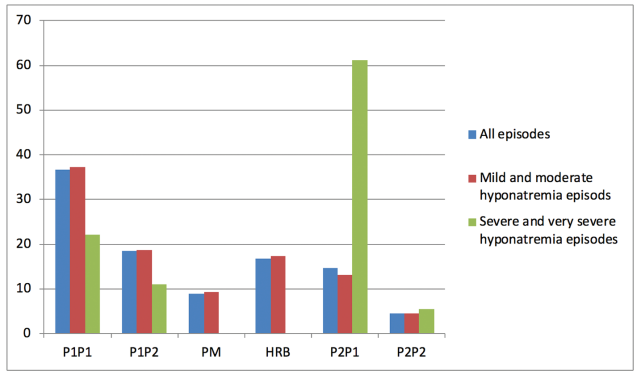
Table I. Comparison of the characteristics of the patients with mild-to-moderate and severe-to very severe hyponatremia

	Patients with mild and moderate hyponatremia	Patients with severe and very severe hyponatremia	p
Age (median) month	59	138	0.003
Gender (male/female)	1.36	1.8	NS
Risk stratification			
HR MR SR	27 (34.6%) 30 (38.5%) 21 (26.9%)	8 (57.1%) 3 (21.4%) 3 (21.4%)	NS
Patients treated with BMT	10/78 (12.8%)	1/14 (7.1%)	NS
Relapsed patients	11/78 (14.1%)	4/14 (28.6%)	NS
hyperglycemia	8/92 patients (8.7 %)	3/14 patients (21.4 %)	NS
Hyperglycemia episodes	28/600 (4.7%)	4/18 (22.2%)	NS
Survival	66/78 (84%)	12/14 (88.2%)	NS

BMT: Bone marrow transplantation, SR: Standard risk, HR: High risk, MR: Median risk

Discussion

Hyponatremia affects approximately 15-30% of hospitalized patients, both children and adults, with a prevalence of 1-8% in the ambulatory setting (1,3,17). The majority of hospital acquired hyponatremia in children is iatrogenic and due in large part to the administration of hypotonic fluids to patients with elevated AVP levels. In recent prospective studies, it was shown that the administration of 0.9% sodium chloride in maintenance fluids can prevent the development of hyponatremia in hospitalized patients (8,18-20). Although isotonic fluids were used as an intravenous maintenance fluid in the presented series, the frequency of hyponatremia was found to be very high. Hyponatremia was most commonly detected in the first part of the induction treatment, protocol I phase I. During this treatment period, patients were completely hospital dependent and they were given intravenous fluids without oral Na restriction. It is obvious that this population has so many risk factors for hyponatremia other than intravenous hypotonic fluids. Oral feeding intolerance, renal



P1P1: Protocol 1 Phase1, P1P2: Prorocol1, Phase2, PM: Protocol M, HRB: High Risk Blocks, P2P1: Protocol2Phase1, P2P2: Protocol2, Phase2

Figure 1. Distrubition of hyponatremia episodes during treatment protocol

Table II. Comparison of the frequencies of mild-to-moderate and severe-to-very severe hyponatremia episodes in different stages of treatment protocol

Treatment period	Total hyponatremia episodes n=618 (%)	Mild or moderate hyponatremia episodes n=600 (%)	Severe or very severe hyponatremia episodes n=18 (%)	p
Protocol 1 phase 1	227 (36.7)	224 (37.3)	3 (16.7)	0.044
Protocol 1 phase 2	114 (18.5)	112 (18.7)	2 (11.1)	NS
Protocol M	55 (8.9)	55 (9.2)	0 (0)	NS
HR blocks	104 (16.8)	104 (17.3)	0 (0)	NS
Protocol 2 phase 1	90 (14.6)	79 (13.2)	11 (61.1)	0.002
Protocol 2 phase 2	28 (4.5)	26 (4.3)	2 (11.1)	NS

HR: High risk, n: Number, NS: Not significant

tubulopathy causing Na loss, and SIADH most probably resulting from drugs were identified as the main factors in children with ALL in this study.

Recent studies have revealed that even asymptomatic hyponatremia is associated with deleterious consequences. It is an independent risk factor for mortality and is also associated with increased length of hospitalization. Even mild chronic hyponatremia can result in subtle neurological impairment and bone demineralization. There is emerging evidence that hyponatremia may alter the immune response, which could explain the increased rate of infections in hyponatremic patients (9-12,21-25). Therefore, hyponatremia should be evaluated immediately even if it is detected as only a laboratory finding. With this aim, we designed this study and the results showed a very high incidence of hyponatremia in children with ALL receiving intensive chemotherapy. Most of the episodes were seen as only a laboratory abnormality. However, the Na intake of those patients with hyponatremia was increased after the detection of hyponatremia.

Although SIADH is a rare cause of hyponatremia in acute leukemia patients, it can occur. Chemotherapy induced nausea and pulmonary infections are important stimuli of ADH release. In this study, hyponatremia episodes were most commonly seen during Protocol I Phase I and Protocol II Phase I where vincristine was used frequently. Similarly, Janczar et al. (26) showed that vincristine is related with hyponatremia episodes. Triazole and imidazole antifungal agents inhibit the metabolism of vincristine through cytochrome P450, leading to excess vinca alkaloid exposure, and severe neurotoxicity, hyponatremia/SIADH, autonomic neuropathy, and seizures. There are several case presentations in the literature emphasizing adverse interactions between antifungal azoles and vincristine. Most are related to itraconazole (27,28). Voriconazole and posaconazole are used in clinical practice very frequently and increased vincristine neurotoxicity has been reported with these drugs as well (29-32). The treatment of hyponatremia includes volume restriction, and/or administration of 0.9% saline with furosemide. In patients with neurological findings, 3% NaCl administration is recommended. The most serious complication of hyponatremia is hyponatremic encephalopathy (5,16,30-32). Children are at significantly higher risk of developing hyponatremic encephalopathy than adults (2,19,33). The most consistent clinical features of hyponatremic encephalopathy are headache, nausea and vomiting. The absence of CT evidence of cerebral edema does not exclude the diagnosis (19). In adults with hyponatremic encephalopathy, the average serum Na level is 111 mEq/L (11,34,35) whereas that in children is 120 mEq/L (34,35).

The results of this study showed that most of the symptoms and findings, such as headache, nausea and vomiting, were not evaluated as a clinical feature of hyponatremic encephalopathy. Although the patients had severe hyponatremia, these findings were overlooked, or they were thought to have been caused by different conditions.

Conclusion

Hyponatremia is very common among children with ALL. Isotonic fluid usage decreases but does not completely solve the problem. Physicians should be aware of the pathogenesis, importance, and treatment of hyponatremia to enhance prevention and early treatment of hyponatremia, as this condition may be harmful even when it is asymptomatic and mild.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent is not required for retrospective studies in Turkey.

Peer-review: Enternally peer-reviewed.

Authorship Contributions

Surgical and Medical Practice: D.Y.K., A.Ş., S.Ö., P.Y.Ö., Z.Ö.S., A.B.A., N.Ö.K., B.K., Data Collection or Processing: A.Ş., S.Ö., P.Y.Ö., Analysis or Interpretation: B.K., Writing: D.Y.K.

Conflict of Interest: All authors declare that they have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Agut Fuster MA, DEL Campo Biosca J, Ferrer Rodriguez A, Ramos Martinez MJ, Viel Martinez JM, Agulles Fornes MJ. Post tonsillectomy hyponatremia: a possible lethal complication. Acta Otorhinolaringol Esp 2006;57:247-50.
2. Arieff AI, Kozniewska E, Roberts TP, Vexer ZS, Ayus JC, Kucharczyk J. Age, gender, and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. Am J Physiol 1995;268:R1143-52.

3. Moritz ML, Ayus JC. Management of hyponatremia in various clinical situations. Curr Treat Options Neurol 2014;16:310.

4. Au AK, Ray PE, McBryde KD, Newman KD, Weinstein SL, Bell MJ. Incidence of postoperative hyponatremia and complications in critically-ill children treated with hypotonic and normotonic solutions. J Pediatr 2008;152:33-8.

5. Duke T, Kinney S, Waters K. Hyponatremia and seizures in oncology patients associated with hypotonic intravenous fluids. J Pediatr Child Health 2005;41:685-6.

6. Miltiadous G, Christidis D, Kalogirou M, Elisaf M. Causes and mechanisms of acid-base and electrolyte abnormalities in cancer patients. Eur J Int Med 2008;19:1-7.

7. Moritz MI, Ayus JC. Preventing neurological complications from dysnatremias in children. Pediatr Nephrol 2005;20:1687-700.

8. Yung M, Keeley S. Randomized controlled trial of intravenous maintenance fluids. J Paediatr Child Health 2009;45:9-14.

9. Al-Dahhan J, Haycock GB, Nichol B, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates. III. Effect of salt supplementation. Arch Dis Child 1984;59:945-50.

10. Al-Dahhan J, Jannoun L, Haycock GB. Effect of salt supplementation of newborn premature infants on neurodevelopmental outcome at 10-13 years of age. Arch Dis Child Fetal Neonatal Ed 2002;86:F120-F3.

11. Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA 1999;281:2299-304.

12. Renneboog Bİ Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, attention deficits. Am J Med 2006;119:e71-e8.

13. Filippatos TD, Milionis H, Elisaf MS. Alteration in electrolyte equilibrium in patients with acute leukemia. Eur J Hematol 2005;75:449-60.

14. Milionis HJ, Bourantas CL, Siamopoulos KC, Elisaf MS. Acid-base and electrolyte abnormalities in patients with acute leukemia. Am J Hematol 1999;62:201-7.

15. O'Regan S, Carson S, Chesney RW, Drummınd KN. Electrolyte and acid-base disturbances in the management of leukemia. Blood 1977:49;345-56.

16. Osior FH, Berkley JA, Newton CR. Life threatening hyponatremia and neurotoxicity during chemotherapy for Burkitt's lymphoma. Trop Doct 2006;36:177-8.

17. Moritz ML, Ayus JC. Hospital- acquired hyponatremia-why are hypotonic parenteral fluids still being used? Nat Clin Pract Nephrol 2007;3:374-82.

18. Montanana PA, Medsto i Alapont V, et al. The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics: a randomized, controlled open study. Pediatr Crit Care Med 2008;9:589-97.

19. Moritz ML, Ayus JC. New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children. Pediatr Nephrol 2010;25:1225-38.

20. Saba TG, Fairbairn J, Houghton F, Laforte D, Foster BJ. A randomized controlled trial of isotonic versus hypotonic maintenance intravenous fluids in hospitalized children. BMC Pediatrics 2011;11:82-90.

21. Ertl T, Hadzsiev K, Vincze O, Pytel J, Szabo I, Sulyok E. Hyponatremia and sensorineural hearing loss in preterm infants. Biol Neonate 2001;79:109-12.

22. Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM 2008;101:583-8.

23. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-26.

24. Murphy DJ, Hope PL, Johnson A. Neonatal risk factors for cerebral palsy in very preterm babies: case control study. BMJ 1997;314:404-8.

25. Shirazki A, Weintraub Z, Reich D, Gershon E, Leshem M. Lowest neonatal serum Na level predicts sodium intake in low birth weight children. Am J Physiol Regul Integr Comp Physiol 2007;292:R1683-R9.

26. Janczar S, Szewczyk BZ, Mlynarski W. Severe hyponatremia in a single-center series of 84 homogenously treated children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2017;39:54-8.

27. Kamaluddin M, McNally P, Breatnach F, et al. Potentiation of vincristine toxicity by itraconazole in children with lymphoid malignancies. Acta Paediatr 2001;90:1204-7.

28. Moriyama B, Henning SA, Leung J, et al. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. Mycoses 2012;55:290-7.

29. Eiden C, Palanzuela G, Hillaire Buys D, et al. Posaconazole increased vincristine neurotoxicity in a child: a case report. J Pediatr Hematol Oncol 2009;31:292-5.

30. Hamdy DA, El-Geed H, El-Salem A, Zaidan M. Posaconazole-vincristine coadministration triggers seizure in a young female adult: a case report. Case Rep Hematol 2012;2012:343742.

31. Jain S, Kapoor G. Severe life threatening neurotoxicity in a child with acute lymphoblastic leukemia receiving posaconazole and vincristine. Pediatr Blood Cancer 2010;54:783.

32. Mahapatra M, Kumar R, Choudhry VP. Seizures as an adverse drug reaction after therapeutic dose of vincristine. Annals of Hematology 2007;86:153-4.

33. Arieff AI, Kozniewska E, Roberts TP, Vexer ZS, Ayus JC, Kucharczyk J. Age, gender, and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. Am J Physiol 1995;268:R1143-52.

34. Bruce RC, Kliegman RM. Hyponatremic seizure secondary to oral water intoxication in infancy: association with commercial bottled drinking water. Pediatrics 1997;100:E4.

35. Sarnaik AP, Meert K, Hackbarth R, Fleischmann L. Management of hyponatremic seizure in children with hypertonic saline: a safe and effective strategy. Crit Care Med 1991;19:758-62.