Original Article

Prevalence and pathophysiology of hypokalemia among adult patients with dengue viral infection

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Abstract

Background: Dengue viral infection (DVI) is one of the major public health problems in Thailand and many parts of the world. Renal complications and electrolyte imbalances in DVI have reportedly increased. Even though the prevalence of hypokalemia is common, the mechanisms of hypokalemia remain uncertain.

Methods: This study employed a retrospective cross-sectional design to investigate admitted patients with DVI at the Division of Medicine, Hat Yai Hospital, Songkhla from 2011 to 2016. This investigation included patients who were 1) ≥15 years 2) admitted at the Internal Medicine Division with DVI dependence on clinical appearances and confirmed by either dengue NS1 antigen or IgM antibody to dengue infection. Patients with pre-existing renal disease and prescribed diuretics were excluded from this study.

Results: This study included 383 patients. The mean serum potassium concentration was 3.75±0.53 mEq/L. and hypokalemia developed among 129 patients (33.7%). Hypokalemia was mild and moderate among 121 (93.8%) and 8 (6.25) patients, respectively. This study demonstrated that age, clinical manifestations, and virus serotypes did not differ between hypokalemia and nonhypokalemia cases. Hypokalemia occurred more frequently among females. Six patients with hypokalemia were additionally investigated. Five patients were female and experienced DHF grade I. Interestingly, these 5 patients had urine potassium to creatinine ratio higher than 13 mEq/gCr and all patients had transtubular potassium gradient higher than 3.

Conclusion: Hypokalemia was common among adult patients with dengue virus but not associated with severity of illness or clinical manifestations. The proposed mechanism of hypokalemia was due to renal loss.

Keywords: hypokalemia, dengue viral infection, electrolyte imbalance

Original Article

ความชุกและกลไกการเกิดภาวะโพแทสเซียมในเลือดต่ำในผู้ใหญ่ที่ป่วยเป็นไข้เลือดออก

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บทคัดย่อ

บทนำ: โรคไข้เลือดออกเป็นปัญหาสาธารณสุขที่สำคัญของไทยและหลายส่วนของโลก การเกิดภาวะแทรกซ้อนทางไตและความผิดปกติของเกลือแร่มีรายงานเพิ่มขึ้นเรื่อย ๆ ภาวะโพแทสเซียมในเลือดต่ำพบได้บ่อย แต่กลไกการเกิดยังไม่ทราบชัดเจน

วิธีการศึกษา: การศึกษานี้เป็นการศึกษาแบบภาคตัดขวางย้อนหลังในผู้ป่วยโรคไข้เลือดออกที่รับไว้ในแผนกอายุรกรรมของโรงพยาบาลหาดใหญ่ สงขลา ในปี พ.ศ. 2554-2559 เกณฑ์คัดผู้ป่วย ได้แก่ 1) ผู้ป่วยอายุมากกว่ากับ 15 ปี 2) ผู้ป่วยไข้เลือดออกที่วินิจฉัยโดยอาศัยลักษณะทางคลินิกร่วมกับการตรวจพบ NS1 หรือ IgM antibody ต่อเชื้อไข้เลือดออก โดยผู้ป่วยที่มีโรคไตอยู่ก่อนหรือได้รับยาขับปัสสาสะจะถูกคัดออกจากการศึกษา

ผลการศึกษา: การศึกษานี้รวบรวมผู้ป่วยจำนวน 383 ราย ค่าเฉลี่ยของระดับโพแทสเซียมในเลือด คือ 3.75±0.53 mEq/ลิตร พบภาวะโพแทสเซียมในเลือดต่ำ 129 ราย (ร้อยละ 33.7) จำแนกเป็นชนิดรุนแรงน้อยและปานกลาง จำนวน 121 (ร้อยละ 93.8) และ 8 (ร้อยละ 6.25) ราย ตามลำดับ การศึกษานี้พบว่า อายุและลักษณะทางคลินิก รวมทั้งชนิดของ dengue serotype ของผู้ป่วยที่เกิดและไม่เกิดภาวะโพแทสเซียมในเลือดต่ำแตกต่างกัน ผู้ป่วยภาวะโพแทสเซียมในเลือดต่ำพบบ่อยในผู้ป่วยเพศหญิง ผู้ป่วย 6 ราย ได้รับการตรวจเพิ่มเพื่อหาสาเหตุของภาวะโพแทสเซียมในเลือดต่ำ พบว่า 5 ราย มีค่าของอัตราส่วนระหว่างโพแทสเซียมในปัสสาวะต่อครีแอทินินในปัสสาวะสูงกว่า 13 mEq/กรัมของครีแอทินิน และทุกรายมีค่าของ transtubular potassium gradient สูงกว่า 3

สรุป: ภาวะโพแทสเซียมในเลือดต่ำเป็นความผิดปกติที่พบบ่อยในผู้ใหญ่ที่ป่วยเป็นไข้เลือดออก ไม่สัมพันธ์กับลักษณะทางคลินิกและความรุนแรงของโรคไข้เลือดออก กลไกการเกิดภาวะโพแทสเซียมในเลือดต่ำเชื่อว่าเกิดจากความผิดปกติของท่อไตทำให้ขับโพแทสเซียม

คำสำคัญ: โพแทสเซียมในเลือดต่ำ, ไข้เลือดออก, ความผิดปกติของเกลือแร่

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Background

Dengue viral infection (DVI) is one of the major public health problems in Thailand and many parts of the world. DVI is caused by a virus of the Flaviviridae family and the 4 different serotypes are labeled DEN-1, DEN-2, DEN-3, and DEN-4. Clinical manifestations of DVI vary highly from asymptomatic to multi-organ dysfunction and death. Renal complications and electrolyte imbalances in DVI were reportedly increased.[1,2] Among electrolyte disturbances, hyponatremia is the most common electrolyte abnormality in DVI.[1-3] The prevalence of hyponatremia accounted for as high as 72%.[1] Hypokalemia commonly occurred as well. The prevalence of hypokalemia ranges from 13 to 42.1%.[3-4] Most patients with hypokalemic experience mild and asymptomatic conditions. However, some patients developed hypokalemic quadriparesis.[5] The mechanisms of hypokalemia remain uncertain due to no obvious explanation for the hypokalemia such as poor intake, medication, or gastrointestinal loss. The proposed mechanisms included potassium redistribution within cells, poor intake, and tubular renal loss due to activation of rennin-angiotensin and aldosterone systems from volume depletion.[1] Moreover, studies have investigated the risk factors and mechanisms of hypokalemia among adult patients with DVI. This study aimed to determine the prevalence and the mechanisms of hypokalemia among adult patients admitted with DVI.

Methods

Study Population

This study employed a retrospective cross-sectional design investigating admitted patients with DVI at the Division of Medicine, Hat Yai Hospital, Songkhla from 2011 to 2016. This investigation included patients who were 1) ≥15 years old, 2) admitted at the Internal Medicine Division with DVI dependence on clinical appearances and confirmed by either dengue NS1 antigen or IgM antibody to dengue. Patients with pre-existing renal disease and prescribed diuretics were excluded from this study. Patients with dengue fever (DF) and dengue hemorrhagic fever (DHF) were graded using World Health Organization criteria.[6] Patients with DHF were arranged in three groups: grade I as mild DHF, grade II as moderate DHF, and grades III to IV as severe DHF.

Data Collection

Serum sodium, potassium, chloride, and bicarbonate were measured by indirect ion-selective electrode and enzymatic kinetic UV assay using an automate analyzer. Hypokalemia was diagnosed when serum potassium concentration was less than 3.50 mEq/L. It could be classified as mild 3.1 to 3.5 mEq/L, moderate 2.5 to 3.0 mEq/L and severe <2.5 mEq/L. Hyponatremia was categorized as a serum sodium level <135 mEq/L. Metabolic acidosis and alkalosis were classified when serum HCO3 levels reachep <18 and >24 mEq/L, respectively. Transtubular potassium gradient (TTKG) and potassium to creatinine ratio were calculated. PCR was also performed from 2013 to 2014. The study was approved by the Institutional Review Board of Hat Yai Hospital.

Statistical analysis

The chi-squared test was used to compare the prevalence of categorical data between patients with hypokalemia and those without. Continuous parameters were compared between patients with hypokalemia and those without using the two-independent t-test and Mann-Whitney U test when appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

The study included 383 patients. The mean age was 29.74±12.46 years, and 217 patients (56.7%) were female. Among all patients, 318 (83.0%) were NS1 positive, 150 (39.2%) were IgM positive, and 85 (22.2%) were both NS1 antigen and IgM positive. DF and DHF were diagnosed in 66 (17.2%) and 317 (82.8%) patients, respectively. The mean serum potassium concentration was 3.75±0.53 mEq/L, and hypokalemia developed among 129 patients (33.7%). Hypokalemia was mild and moderate in 121 (93.8%) and 8 (6.25%) patients, respectively, while four patients had serum potassium level more than 5.5 mEq/L.

The attributes of patients with and without hypokalemia are summarized in **Table 1.** No significant differences were observed in the medium age, proportion of

vomiting, diarrhea, and the severity of DVI among patients with and without hypokalemia (p value >0.05). Hypokalemia occurred more frequently among females. The prevalence of hypokalemia was 31.8% among patients with DF and 34.1% among patients with DHF; without significant difference (p value = 0.725). The prevalence of hypokalemia in different severity levels of DHF was comparable.

Table 1. Comparison of demographic data and clinical manifestations of non-hypokalemic and hypokalemic groups

	Non-hypokalemia (n = 254)	Hypokalemia (n = 129)	P value
Age (median±IQR)	26.0±19.0	26.0±14.0	0.994
Sex, male (%)	122 (48.0)	44 (34.1)	0.009
Patients with vomiting (%)	123 (48.4)	50 (38.8%)	0.072
Patients with diarrhea (%)	67 (26.4)	26 (20.2%)	0.179
Dengue fever, (%)	45 (17.7)	21 (16.3)	0.725
Dengue hemorrhagic fever: • mild (%) • moderate (%) • severe (%)	 133 (52.4) 43 (16.9) 33 (13.0)	 64 (49.6) 23 (17.8) 21 (16.3)	0.794

The initial laboratory findings of patients with and without hypokalemia are shown in **Table 2.** Patients with hypokalemia had expectedly lower serum potassium levels of 3.3±0.2 mEq/L than those without hypokalemia of 3.9±0.5 (P<0.001). No significant differences were observed in white blood cell count, platelet count, bicarbonate level, and albumin concentrations between the two groups (**Table 2**).

Table 2. Comparison of initial laboratory findings of non-hypokalemia and hypokalemia groups

	Non-hypokalemia (n = 254)	Hypokalemia (n = 129)	P value
Hematocrit (%)	41.15±8.95	40.20±7.65	0.045
White blood cells (/µL)	3,825.0±3,545.0	3,750.0±3,285.0	0.408
Platelet count (/µL)	61,000±88750	58,000±71,500	0.613
Sodium (mEq/L)	136.0±4.0	137.0±5.0	0.022
Potassium (mEq/L)	3.9±0.5	3.3±0.2	<0.001
Chloride(mEq/L)	103.0±7.0	104.0±7.0	0.003
Bicarbonate (mEq/L)	23.0±5.0	23.0±0.5	0.916
BUN (mg/dL)	11.0±7.0	10.0±5.0	<0.001
Creatinine (mg/dL)	0.81±0.34	0.69±0.32	0.001
Albumin (g/dL)	3.71±0.62	3.70±0.70	0.667
Prevalence			
Hyponatremia (%)	88 (34.6)	34 (26.4)	0.10
Metabolic alkalosis (%)	78 (30.7)	38 (29.5)	0.801
Type of DEN Virus (%) DEN-1 DEN-2 DEN-3 DEN-4	 2 (5.3%) 2 (5.3%) 18 (47.4%) 16 (42.1%)	 1 (4.3%) 2 (4.3%) 9 (39.1%) 12 (52.2%)	0.9

Abbreviation: µL; microliters, mEq/L; milliequivalent per liters, mg/dL; milligram per deciliters, g/dL; gram per deciliters

Although both groups had different sodium and chloride levels, the proportion of hyponatremia and metabolic alkalosis did not significantly different between patients with hypokalemia and those without. Hematocrit level, BUN, and serum creatinine levels were slightly lower but statistically significant in the hypokalemic group. Among 62 patients, further investigated for type of dengue serotypes, the majority were DEN-3 and DEN-4. No relationship was found between type of DEN and the occurrence of hypokalemia.

Six patients with hypokalemia were additionally tested to explain the mechanisms of hypokalemia. Five patients were female and experienced DHF grade I. Interestingly, five patients had urine potassium to creatinine ratio higher than 13 mEq/g Cr and all patients had TTKG higher than 3 (**Table 3**).

Table 3. Clinical and laboratory findings in the patients with hypokalemia

Case	Age	Sex	Diagnosis	Serum K	Urine K	TTKG*	Urine K/Cr (mEq/g)
1	28	F	DHF grade 1	3.2	14.0	3.6	7.8
2	40	F	DHF grade 1	3.18	82.8	8.9	33.2
3	28	F	DHF grade 1	3.41	47.4	13.9	20.3
4	43	F	DHF grade 1	3.3	40.0	5.4	23.3
5	16	F	DHF grade 1	3.2	40.0	7.8	28.8
6	42	M	DF	3.3	46.0	5.2	16.6

** The trans-tubular potassium gradient (TTKG) = (urine K × plasma osmolality / serum K × urine osmolality)*
Abbreviation: K; potassium, TTKG; the trans-tubular potassium gradient, Cr; creatinine, mEq/g; milliequivalent per gram, F; female, M; male, DHF; dengue hemorrhagic fever.

Discussion

We found that the prevalence of hypokalemia among adults admitted with DVI was about one third. No associations were found between hypokalemia and the clinical severity and serotype of DVI. Patients with hypokalemia were more common among females, and those with lower BUN and serum creatinine levels. An additional investigation showed the cause of hypokalemia was due to tubular renal loss, at least in mild severity cases.

In this study, the prevalence of hypokalemia among adults admitted with DVI was 33.7%. One study among children found the prevalence of hypokalemia was only 15.3%[3], while one study among adults showed a high incidence of 42.6%.[4] The prevalence of hypokalemia seemed to be higher among adults. However, age-related differences in prevalence of hypokalemia were poorly explained and data on clinical features among adult patients remain limited.[7] Hypokalemia was mild and asymptomatic in the majority of patients in most studies. In this study, no case of severe hypokalemia was found, and no symptoms were related to hypokalemia. However, dengue-associated hypokalemic paralysis could not be ignored.

Reports on the relationship between the prevalence of hypokalemia and the severity of DVI were conflicting. Some reports including the report in this study demonstrated that the mean serum potassium concentration and prevalence of hypokalemia were unrelated to severity, defined as DF vs DHF, of DVI.[3,8] Whereas Khandelwal Vinay G4 showed that mild hypokalemia was more common in DF compared with DHF whereas moderate and severe hypokalemia were more common in DHF. However, when statistical analysis was performed, the p-value was without significance, and hypokalemic quadriparesis was reported in mild DVI.[9]

In this study, factors associated with the occurrence of hypokalemia included being female, and BUN and

creatinine levels. Several factors may influence disease manifestations, including host factors, virus serotype or genotype, sequence of virus infection, and differences in dengue cross-reactive antibody and T-cell responses.[10] The explanation for the susceptibility of females developing hypokalemia remain unclear. These factors had not been mentioned before. Although the results of BUN and creatinine significantly differed, clinical significance improbable because their levels differed slightly and remained within the normal range.

The pathophysiology behind developing hypokalemia among these patients was not well understood. Hypokalemia can be caused by redistribution, low potassium intake, or excessive loss of potassium in the urine or through the GI tract. Factors that cause redistribution such as metabolic alkalosis and severity of DVI and the issue of GI loss in this study did not appear. Patients with hypokalemia did not present diarrhea or vomiting more frequently. In addition, six patients with hypokalemia and additional tests showed that all patients had a TTKG greater than 3 or urine potassium to creatinine ratio greater than 13 mEq/g Cr, indicating tubular potassium loss. Thus, this study found that the mechanism of hypokalemia was caused at least by renal tubular loss. A combination of mechanisms may be responsible for the hypokalemia observed in dengue cases.

The limitations encountered of this study included first, this research was based on a single center retrospective observational study. Second, the dengue serotype of 24 patients was unable to be identified. Third, the analysis using the univariable model without adjusting confounders might have caused limit generalizability. Last, only six patients joined an additional urine study to further investigate the cause of hypokalemia.

Conclusion

Hypokalemia was common among adult patients with dengue virus. The prevalence of hypokalemia was not associated with severity of illness or clinical manifestations. The proposed mechanism of hypokalemia was due to renal loss.

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