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Traumatic Brain Injury Associated with Hyponatremia

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ABSTRACT

Background: Traumatic brain injury (TBI) is a one of the commonest injuries treated at the Neurosurgery Department. The incidence rate is approximately 3% in the general population and the mortality rate is about 30% of all injury deaths. Hyponatremia leads to high morbidity and/or mortality in TBI patients. Our study discusses the epidemiology of TBI associated with hyponatremia. **Methods:** Retrospective analysis of 80 patients with TBI between February 2017 and November 2018 was performed. The relationship between the incidence of hyponatremia in TBI patients and age, sex, GCS, type, severity of injury and whether the patient was submitted to surgery or not. **Results:** Out of 80 TBI patients recruited for the study, 25 of them suffered from hyponatremia. Hyponatremia following TBI wasn't related to age, sex but it was related to the type of injury, the Glasgow Coma Scale (GCS) score ≤ 8, surgical history. TBI with hyponatremia usually had longer stay in the hospital and bad outcome. **Conclusions:** Sever TBI patients (GCS score ≤ 8), intracranial hemorrhage and/or skull base fracture are susceptible to developing hyponatremia and require additional treatment aiming to normalization of serum sodium levels to prevent deterioration of their condition.

Abbreviations: ANP, Atrial natriuretic peptide; CSWS, Cerebral salt wasting syndrome; SIADH, Syndrome of inappropriate secretion of antidiuretic hormone; TBI, Traumatic brain injury.

Keywords: Traumatic brain injury; Hyponatremia; Cerebral salt wasting syndrome; Syndrome of inappropriate secretion of antidiuretic hormone.

INTRODUCTION

Traumatic brain injury (TBI), means an change in brain functions due to external force[(1)]. It is considered as socioeconomic burden and leads to high morbidity and mortality around the world. It contributes to 30% of all injury-related deaths, its annual cost is around $60 billion in US[(2)]. Hyponatremia is one of the most common electrolyte abnormalities in neurosurgical patients and is often observed in patients with TBI, subarachnoid hemorrhage (SAH), sellar lesions, and intracranial infection[(3)]. It is more common than hypernatremia[(4)]. The incidence of TBI associated with hyponatremia is 33% from all cases of TBI[(5,6)], usually within the first 5 days after cerebral insult[(7)]. SAH is one of the commonest insults associated with hyponatremia, over 50% of patients develop it and about 20% of them experience a decrease in serum sodium concentration to <125 mmol/L. Hyponatremia is a common cause of disability and/or death in TBI patients if not diagnosed and treated as early as possible[(5,6)]. Although acute severe hyponatremia increases inpatient mortality, recent data suggest that even mild degrees of hyponatremia may give an adverse prognosis on different patient groups[(7)].

The common causes of hyponatremia in TBI are inadequate salt intake in the diet, cerebral salt wasting (CSW) and syndrome of inappropriate secretion of antidiuretic hormone (SIADH)[(9)]; one study mentioned that 80% of cases of hyponatremia are secondary to SIADH[(10)].

Hyponatremia in TBI may be due to excess secretion of arginine vasopressin (AVP), adrenocorticotrophic hormone (ACTH) insufficiency, SIADH or CSW and sometimes multifactorial (see table 1). In clinical practice, to prevent cerebral vasoconstriction, we use high volumes of intravenous fluids and it is sometimes complicated by hyponatremia in many neurosurgical units. Although the etiology of hyponatremia in TBI was been studied retrospectively, most of it lack reliable hemodynamic, hormonal and biochemical data to give accurate diagnosis[(7)].

Table 1. The causes and management of neurosurgical hyponatremia[(7)].

Diagnosis	Blood Volume Status	Diagnostic Criteria	Treatment
SIADH	Euvolemic	See Table 2	Fluid restriction
Acute ACTH deficiency	Euvolemic (may be hypotensive)	0900 h cortisol <300 nmol/L in stressed patient	Steroid replacement therapy
Hypovolaemia	Hypovolemic	Negative fluid balance	IV fluids
Cerebral salt wasting syndrome (CSWS)	Hypovolemic	Profound diuresis and sodium loss Low CVP and BP.	Aggressive IV fluids
Mixed SIADH and CSWS	Variable/fluctuating	Usually SIADH initially, then progressing to CSWS	Depends on stage
Inappropriate IV fluids	Hypervolemic	Positive fluid balance, edema/LVF	Diuretics Stop IV fluids

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Table 2. Diagnostic criteria of SIADH[11].

1. Hyposmolality; plasma osmolality <280 mOsm/kg.
2. Increase urinary concentration (Uosm >100 mOsm/kg).
3. Patient is clinically euvolemic.
4. Increase urinary sodium (>40 mmol/L) inspite of normal salt and water intake.
5. Exclude glucocorticoid deficiency and hypothyroidism specially in neurosurgical patients.

Although previous studies have mentioned that SIADH is the main cause of hyponatremia following TBI, recent study refers to acute pituitary dysfunction result in glucocorticoid deficiency as an unfamiliar cause of hyponatremia. Most of patients with moderate/severe TBI, plasma cortisol measurements were done daily, 87% of them with hyponatremia had plasma cortisol concentrations of <300 nmol/l (<10.8 mcg/l), which were lower than a control group of patients [12].

Another cause of hyponatremia in TBI is CSWS. This clinical syndrome was first described in 1950 by Peters et al.[13]. It was seen in TBI, SAH and intracranial aneurysms[14]. Authors mentioned that the brain pathology attenuated the sympathetic innervation of the kidney, causing diuresis, result in a hyponatremia and hypovolemia[8]. A potential condition possibility separated from SIADH that could cause hyponatremia in TBI was discussed in 1981 after a report of 12 unselected patients, who had developed hyponatremia following SAH and TBI[15]. Hyponatremia associated with natriuresis was in 10 patients with evidence of a reduction in blood volume. The authors concluded that there was clear evidence that hypovolemia precluded the diagnosis of SIADH by standard criteria, and raised the possibility of CSWS[8].

Classification of hyponatremia in neurosurgical patients includes:

Hypovolemic hyponatremia: Clinical signs are hypotension, tachycardia, mucous hydration and decreased skin turgor, orthostatism and decreased ocular pressure, if central venous pressure (CVP) measurement is important to diagnosis of hypovolemia. Deceased urinary sodium concentration is a useful marker for hypovolemia. CSW is recognized by hypovolemia with increase of sodium excretion, without other explanations for such finding (e.g. salt-wasting nephropathy or diuretic therapy)[16].

Hypervolemia: Characterized by volume overload with a positive fluid balance and increased CVP are characteristic for diagnosis of hypervolemic hyponatremia and sometimes peripheral or pulmonary edema[10].

Euvolemia: SIADH is a common cause of euvolemic hyponatraemia, where inappropriate secretion of AVP despite plasma hypo osmolality, causing water retention and worsening of hyponatremia[16].

In a prospective study of hospital admissions, the overall mortality was 28% in hyponatremic patients (<125 mmol/l) as compared to 9% in normonatremic controls, and increased up to 50% in patients with serum sodium concentrations <115 mmol/l[17]. In an animal study, even asymptomatic subjects had a subclinical brain edema when the serum sodium was <125 mmol/l[8]. The mortality in patients with severe hyponatremia observed also after their discharge, with a mortality of 20% in hospital and 45% within 6 months of follow-up[18]. In a prospective cohort study on 8142 patients, hyponatremia (<135 mmol/l) was present in 15% of the patients on admission, with an increased risk of mortality even in patients with mild hyponatremia[19].

MATERIALS AND METHODS

This study was done in Alqunfudah General Hospital, Saudi Arabia on the patients who had been admitted in Neurosurgical Department between February 2017 and November 2018.

Ethical approval:

The study was approved by the Ethics Board of the Hospital.

The inclusion criteria comprised: (1) admission to the neurosurgery department within 24 hours after onset of TBI; (2) a GCS score ≤13; and (3) aged between 15 and 65 years old. The exclusion criteria were: (1) pregnancy; (2) additional concurrent injuries, such as bone fractures, chest injuries, urinary tract injuries, or abdominal organ injures; (3) history of liver or kidney disease; (4) history of an adrenal, thyroid, or pituitary disorder; (5) diabetes mellitus; (6) diabetes insipidus (as this condition often causes hypernatremia and sometimes fluctuations from hypernatremia to hyponatremia); and (7) posttraumatic vomiting. The inclusion and exclusion parameters were derived from the medical database of the patients and TBI features (e.g., basal skull fracture) were reconfirmed by evaluating the patients' computed tomography (CT) scans. All patients involved in our study were diagnosed as TBI including: Cerebral contusion (CC), acute epidural hematoma (AEDH), acute subdural hematoma (ASDH), chronic subdural hematoma (CSDH), traumatic subarachnoid hemorrhage (tSAH), skull bone fracture and diffuse axonal injury (DAI). Patients who had more than one diagnosis were classified under the major diagnosis; for example, if patients had skull and AEDH, they were submitted under the AEDH group.

Severe TBI is usually associated by high intracranial pressure[3]. On the basis of the extent of intracranial pressure, mannitol plus furosemide was used to dehydrate and reduce intracranial pressure. Moreover, patients with syndrome of SIADH and CSWS exhibit

hyponatremia, increased urinary sodium, and low blood volume (CSWS only). Patients with significantly reduced blood volume received a blood transfusion to correct the hypovolemia followed by hypertonic saline supplementation to correct the hyponatremia.

Determination of Hyponatremia, SIADH, and CSWS: Blood samples were collected three times; in first, third and seventh days of admission according to the hospital's standard blood collection procedure for patients with TBI. The patient would be diagnosed with hyponatremia if the blood test results fit the hyponatremia criteria at any of these 3 time points. The hyponatremia diagnosis was made when the serum sodium level was <135 mmol/l, where, a serum sodium level of 130 to 135 mmol/L was considered mild hyponatremia, 120 to 130 mmol/l was considered moderate hyponatremia, and <120 mmol/l was considered severe hyponatremia. The diagnostic criteria of SIADH were: Serum sodium level of <130 mmol/l, plasma osmolality of <270 mmol/l, a ratio of urine osmolality to plasma osmolality of >1, urine sodium levels of >20 mmol/l or >80 mmol/24 hours, no kidney, heart, liver, adrenal or thyroid dysfunction, no skin edema or ascites, no hypotension, and no dehydration or other signs of hypovolemia. CSWS encompasses hyponatremia and low blood volume that develop in cases of intracranial lesions due to the sodium loss (through renal clearance) and edema. The diagnostic criteria of CSWS were: serum sodium level of <130 mmol/L after regular salt intake, blood volume of <70mL/kg body weight, urinary sodium of >20 mmol/L or >80 mmol/24 hours, increase in plasma ANP without heart, liver, kidney, adrenal, and thyroid dysfunction. Serum and urine sodium levels and plasma osmolality were determined by routine clinical chemistry. Polyuria was defined as a urine output of >2500ml/24 hours[12].

GCS scoring: GCS scoring was done within 1 hour after admission of the patients to the hospital. A GCS score from 9 to 13 was classified as moderate TBI and a GCS score from 3 to 8 was classified as severe TBI[20].

CT scan: A CT scan of the head was performed within 1 hour after the patients were admitted to the hospital and again after 12 hours. The CT scans were used to check for intracranial hemorrhage, brain contusion, skull fracture, and other injuries. For this study, the presence of brain edema and a basal skull fracture were marked as potential factors contributing to hyponatremia. In addition to the CT scans, other clinical features such as cerebrospinal fluid leaks and cranial nerve injury were also considered indicative for a basal skull fracture[3]. The patients who exhibited these symptoms were therefore included in the study.

Statistical analysis

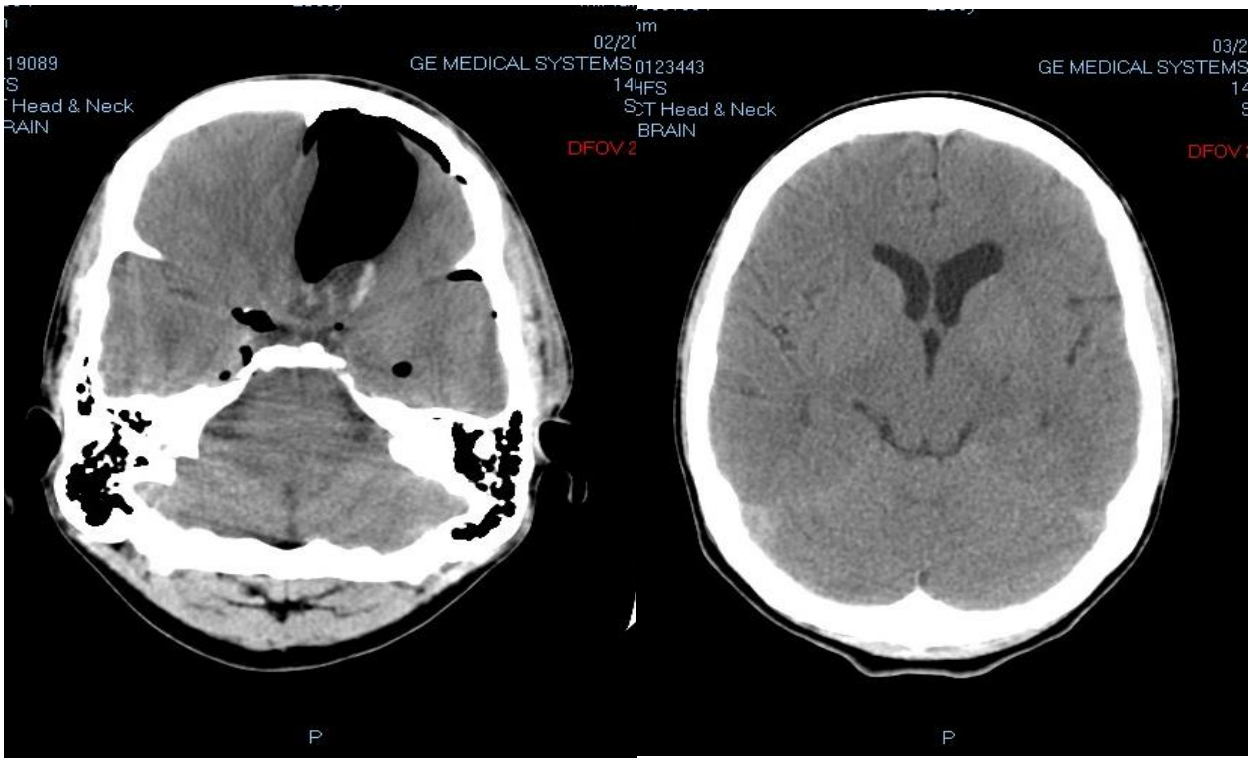
Statistical analysis was performed using SPSS (IBM, Armonk, NY). To analyze the role of age in the development of TBI-associated hyponatremia, the ages of the patients with and without hyponatremia were compared using an unpaired Student *t* test. The relation between the prevalence of hyponatremia in patients with moderate or severe TBI and their age, sex, type of injury, and GCS score, whether the patient underwent surgery, and the presence of cerebral edema, intracranial hemorrhage and basal skull fracture was investigated by univariate analysis using a Pearson x^2 test followed by multivariate logistic regression analysis to determine the association between these factors and hyponatremia.

RESULTS

Patient population and background

In the given period a total of 398 patients were treated in Alqunfudah General Hospital, Saudi Arabia, of which 80 patients (53 males, 27 females; 46.8± 9.7 y of age) were selected based on the specified inclusion and exclusion criteria. Of the 80 patients, 50 patients (62.5%) had moderate TBI (i.e., GCS score of 9 to 13) and 30 patients (37.5%) had severe TBI (i.e., GCS score of 3 to 8. The diagnoses of them were as follows: 24 patients with cerebral concussion, 12 patients with skull bone fracture (2 of them had pneumocephalus and one of these pneumocephalic patient had tension pneumocephalus and treated surgically (figure 1), 5 patients with tSAH, 5 patients with AEDH, 8 patients with ASDH, 11 patients with CSDH, 13 patients with traumatic intracerebral hematoma and CC, 2 patients with DAI.

Among the 80 patients, 25 received surgical treatment. The surgical treatments were as follows: 4 patients underwent bone plastic surgery, 1 patient underwent evacuation of tension pneumocephay, 1 patient of tSAH patients complicated by hydrocephalus and underwent ventriculoperitoneal shunt insertion, 4 patients underwent evacuation of AEDH, 5 patients underwent evacuation of ASDH, 6 patients underwent burr hole and evacuation of CSDH, 4 and patients underwent removal of intracerebral hematoma and evacuation of contused brain.



a) **b)**

Figure no 1: TBI presented by fracture base (ACF), Pneumocephalus and hyponatremia a) preoperative b) postoperative CT brain.

Table 3: Characteristics of patients

Diagnosis	No.	Male/female	Age	Range	Hyponatremia	%
erebral concussion	**24**	**15/9**	**35.5**	**18-61**	**1**	**4.17**
kull bone fracture	**12**	**9/3**	**27.7**	**15-58**	**3**	**25**
AH	**5**	**3/2**	**40.1**	**21-64**	**0**	**0**
EDH	**5**	**4/1**	**32.3**	**16-50**	**3**	**60**
SDH	**8**	**5/3**	**39.4**	**15-65**	**4**	**50**
SDH	**11**	**7/4**	**52**	**19-65**	**6**	**54.5**
CH and CC	**13**	**9/4**	**34.8**	**15-63**	**7**	**53.8**
IA	**2**	**1/1**	**30.2**	**22-43**	**1**	**50**
otal	**80**	**53/27**	**36.5**	**15-65**	**25**	**31.25**

Incidence of hyponatremia

Twenty-five (31.25%) of the 80 patients presented hyponatremia within the admission period. No patients had tSAH, presented with hyponatremia. The incidence of hyponatremia among the other patients were as follows: Cerebral concussion, 1 of 24 patients (4.17%); Skull bone fracture, 3 of 12 (25%); AEDH, 3 of 5 patients (60%); ASDH, 4 of 8 patients (50%); CSDH, 6 of 11 patients (54.5%); CC, 7 of 13 patients (53.8%); and DAI, 1 of 2 patients (50.0%) (Table 3).

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Comparison of patients with and without hyponatremia are mentioned in Table 4. Although the initial assessment by GCS revealed no difference between the patients with and without hyponatremia, most of the patients were presented with hyponatremia during first 3 days of trauma; however, some patients were presented with hyponatremia after 8 days except for patients with CSDH due to unknown onset of trauma in most cases.

Table 4: Characteristics of patients with and without hyponatremia

Hyponatremia	No (n = 55)	Yes (n = 25)
Sex		
Male	36	17
Female	19	8
Age		
Glasgow coma scale		
>8	37	13
≤ 8	18	12
Surgery		
Yes	16	9
No	39	16
Administration period (d)	9.6	16.2
Glasgow outcome scale		
Good recovery	46	13
Moderate disability	5	7
Severe disability	2	2
Vegetative state	1	2
Death	1	1

Causes and clinical presentation of hyponatremia

From the 80 TBI patients, 25 patients (31.25%) developed hyponatremia, of which 6 cases had mild, 12 cases had moderate, 7 cases had severe hyponatremia and there were 8 cases of hypokalemia.

The causes of hyponatremia in the TBI patients were: greater fluid intake, inadequate sodium intake/diuretic use 13 (52%), SIADH 9 (36%), CSWS 3 (12%). The clinical The commonest presentation is reduced consciousness and many patients were presented by multiple symptoms.

Table 5: Presentations of hyponatremia

Clinical manifestation	Number of Patients and percent
Reduced consciousness	9 (36)
Seizures	3 (12)
Mental fatigue, lethargy, and irritability	4 (16)
Anorexia, nausea, and vomiting	3 (12)
Mental and behavioral abnormalities	2 (8)
Other electrolyte imbalance	8 (32)
Polyuria	4 (16)

Treatment of Hyponatremia

For the patients with mild and moderate hyponatremia as a result of insufficient sodium intake and/or excessive administration of diuretics (furosemide): (1) additional sodium was administered orally when possible or otherwise through intravenous infusion of 3% hypertonic saline at a rate of 100 to 150 ml/hour, and/or (2) the administration of diuretics was reduced. During the treatment, the clinical signs of hyponatremia were closely monitored.

Patients with persistently low serum sodium levels were tested for SIADH and CSWS. For patients with SIADH, water intake was limited to 800 to 1000 ml/24 hours, 15 supplemental sodium was provided, and, where necessary, diuretics[21] and/or albumin[22] were administered. Patients with CSWS were given blood transfusion, supplemental sodium, and, where necessary, a short-term treatment with steroids. Mineralocorticoids (e.g., fludrocortisone) could be applied to reduce the excretion of sodium and promote sodium absorption.

Other disorders, such as low serum potassium and chlorine levels and high serum glucose levels, were also treated. Hyponatremia often concurs with other types of disorders such as hypokalemia, hyperglycemia, etc. Consequently, contributory factors to the electrolyte imbalance have to be taken into account when treating hyponatremia.

Serum sodium levels were successfully normalized in 24 out of the 25 TBI patients with hyponatremia. In 1 patient, diagnosed with CSWS, serum sodium levels remained persistently low. For this patient, supplemental sodium was given for 1 month, and, in the meantime, hormone therapy (e.g., cortisone fluoride) was started. Although the patient recovered well, the serum sodium levels remained around 130 mmol/l, so he was referred to a more advanced hospital for further treatment. After 6 months, in the follow-up visit, his serum sodium level was still low at 125 and 131 mmol/l, but the patient showed no clinical symptoms of hyponatremia.

DISCUSSION

Hyponatremia in clinically ill patient is associated with longer stay in ICU and increased mortality rate[(23)]. The prevalence of hyponatremia used to be as high as 30 - 40% among ICU patients and up to 50% in neurosurgical patients[(24)]. Previous studies have suggested that 27 – 41% of TBI patients develop hyponatremia [(25, 26)] and 51% of TBI develop mild hyponatremia whoever 20 % of them develop moderate and severe hyponatremia[(27)]. Another study proved that TBI patients develop hyponatremia only in 16.8 %[(25)]. In our study the percent was 31.25 % of patients. The prevalence of hyponatremia following TBI was not associated with age, sex, and type of injury of the patient, or whether the patient underwent surgery. The

manifestation of hyponatremia was strongly associated with the GCS score, the presence of cerebral edema, and the presence of a basal skull fracture[25,28]. In the present study, it seems that the presence of hyponatremia doesn't correlate well with GCS score on arrival. Conversely, cranial fractures, greater fluid intake and inadequate sodium intake from day 1 to 3 were found to be risk factor for hyponatremia in TBI patients, regardless of type of TBI or the patient's injury severity score, which are indicative of anatomical severity of injury. during the first week of trauma, appropriate fluid management is important[29]. SIADH and CSWS are considered to be 2 principle causes of hyponatremia in TBI patients. While several studies reported CSWS to be a more common cause for hyponatremia in neurosurgical patients than SIADH[30,31], we found the opposite with SIADH in 36% of the cases and CSWS in 12% of the cases.

The mechanisms underlying the increased risk of hyponatremia in some TBI patients remain unclear to date. On the basis of our finding that a GCS score ≤ 8, cerebral edema, and a basal skull fracture are important risk factors for hyponatremia, we speculate that this may be related to the following mechanisms. First, patients with severe TBI often have subarachnoid hemorrhage, which can cause obstruction of the cerebrospinal fluid circulation, leading to cerebral edema and/or increased intracranial pressure. An increased intracranial pressure disturbs the local blood circulation, which causes mechanical irritation or ischemia of the hypothalamic osmoreceptors, leading to excessive secretion of ADH and thereby dilutional hyponatremia[32]. Second, some forms of brain damage with hypothalamopituitary axis impact (e.g., edema, traumatic and aneurysmal subarachnoid hemorrhage and ischemia) will lead to water-electrolyte disorders. Third, cerebral edema and local edema at/near the hypothalamus disturb the local blood circulation, which stimulates the hypothalamus and leads to hyponatremia. Fourth, a basal skull fracture leads to pituitary stalk damage, which causes hypothalamic dysfunction and consequent hyponatremia. Finally, a basal skull fracture causes cerebrospinal fluid leakage and/or intracranial infection, changing the quality and quantity of cerebrospinal fluid. This disrupts the internal environment of the neurons, causing dysfunction of the hypothalamus, in turn leading to hyponatremia[31].

CONCLUSIONS

In conclusion, TBI patients with a GCS score ≤ 8, intracranial hemorrhage and/or a basal skull fracture are particularly prone to hyponatremia and require additional attention to normalize their serum sodium levels to prevent deterioration of their condition.

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