Acute lower limb ischemia is a frequent complication of severe diabetic hyperosmolarity

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Aim. – To describe the outcome of intensive care unit (ICU) patients admitted with a hyperglycaemic hyperosmolar non-ketotic syndrome (HHNS), with a specific analysis of precipitating conditions and complications including lower limb ischemia.

Methods. – Retrospective review of patients admitted in a university-hospital ICU for HHNS.

Results. – Seventeen consecutive patients (9F/8M; age: 75 years [57–81] (median [25–75% percentiles]; Glasgow Coma score: 13 [12–14]) were admitted for HHNS over an 8-year period (1998–2005). On admission, the blood glucose level was 40.0 mmol/l [26.3–60.8], the corrected serum sodium concentration 167 mmol/l [158–174], and the calculated plasma osmolarity 384 mosmol/l [365–405]. All the patients presented with renal failure due to severe dehydration. An infection was identified as the precipitating factor in 8/17 cases. Three (18%) patients died in the ICU. Non-survivors were significantly older than survivors (P = 0.02). Using univariate analysis, no other parameter measured on admission was related to mortality. Four patients (24%) presented with lower limb ischemia. They had a significantly more elevated blood urea nitrogen (P = 0.03), creatinine phosphokinase level (P = 0.04), and leukocyte count (P = 0.02). The bilateral, symmetrical, and distal extremity involvement suggested diminished blood flow due to hyperviscosity, hypotension, vasoconstrictors, or cholesterol emboli rather than a proximal arterial obstruction as causative mechanisms. No patient was treated surgically. Ischemia reversed with fluid loading and resulted in toe dry digital necrosis.

Conclusion. – HHNS is a rare but life-threatening cause of ICU admission. There is a high incidence of lower limb ischemia in HHNS patients, which may be related to dehydration and blood hyperviscosity.

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Résumé

L’ischémie aiguë des membres inférieurs est une complication fréquente du coma hyperosmolaire diabétique.

Objectif. – Décrire le devenir de patients admis en réanimation pour coma hyperosmolaire avec une analyse plus spécifique des facteurs favorisants et des complications dont l’ischémie aiguë des membres inférieurs.

Méthodes. – Analyse rétrospective des patients admis pour coma hyperosmolaire dans une unité de réanimation d’un hôpital universitaire.

Résultats. – Dix-sept patients consécutifs (9F/8H; âge : 75 ans [57–81] (médiane [percentiles 25–75 %]; Score de Glasgow : 13 [12–14]) ont été admis pour coma hyperosmolaire sur une période de huit ans (1998–2005). À l’admission, la glycémie était à 40,0 mmol/l [26,3–60,8], la natrémie corrigée de 167 mmol/l [158–174] et l’osmolarité sanguine calculée de 384 mosmol/l [365–405]. Tous les patients présentaient une insuffisance rénale en rapport avec une déshydratation sévère. Un épisode infectieux était trouvé comme facteur déclenchant dans 8/17 cas. En réanimation, 3/17 (18 %) patients sont décédés. Les patients décédés étaient significativement plus âgés que les survivants (P = 0,02). En analyse univariée, aucun autre paramètre mesuré à l’admission n’était lié au décès. Quatre patients (24 %) présentaient une ischémie aiguë des membres inférieurs. Ils avaient une urémie (P = 0,03), une créatinine phosphokinase (P = 0,04), et une leucocytose (P = 0,02) significativement plus élevées. Le caractère bilatéral, symétrique et distal de l’ischémie des extrémités plaidait pour un mécanisme en rapport avec une baisse de perfusion de la circulation sanguine...
tissulaire dû à l’hyperviscosité, l’hypotension, les vasoconstricteurs ou d’éventuels embols de cholestérol, plutôt qu’une artérite ou une obstruction artérielle proximale. Aucun patient n’a été opéré. L’ischémie s’est résolue avec le remplissage vasculaire et a évolué vers une nécrose sèche pulpaire des orteils.

Conclusion. — Le coma hyperosmolaire est un motif rare mais grave d’admission en réanimation. Il existe chez ces patients, une incidence élevée d’ischémie aiguë des membres inférieurs, en relation probable avec la déshydratation et l’hyperviscosité sanguine.

Keywords: Diabetes; Hyperosmolar non-ketotic diabetic syndrome; Lower limb ischemia; Mortality; Outcome

Mots clés : Diabète ; Coma Hyperosmolaire ; Ischémie aiguë des membres inférieurs ; Mortalité ; Pronostic

1. Introduction

Diabetic hyperosmolarity is a common metabolic complication of uncontrolled type 2 diabetes, with an estimated incidence of about 17.5 cases/100,000 per year [1]. In elderly patients with already limited physical and cognitive autonomy, this metabolic disorder usually results in devastating effects [2]. Elevated 10–40% mortality rates were reported, in relation to age and significant morbidities, contrasting with the emergencies associated with diabetic ketoacidosis [3–6]. However, final outcome is thought to be more directly related to the underlying precipitating factors, hemodynamic status, and non-specific complications of coma rather than age, blood glucose level or osmolarity [4,5,7–9]. Hyperosmolarity frequently occurs in the setting of bacterial pneumonia, myocardial infarction, stroke, or thromboembolic complications, which usually are the cause of death [4,10,11].

Peripheral occlusive vascular disease is also common in diabetic patients, often resulting in foot ulceration and lower extremity amputation. Diabetes mellitus is an independent risk factor associated with a higher prevalence of chronic critical lower limb ischemia [12]. Due to severe dehydration, diabetic patients with hyperosmolar emergencies are at increased risk of developing vascular thrombosis including cerebral and mesenteric artery occlusions [13,14]. However, the incidence of acute lower limb ischemia in these patients has been poorly reported. Here, we report the outcome of hyperglycemic hyperosmolar non-ketotic diabetic syndrome (HHNS) in a medical intensive care unit (ICU), emphasizing precipitating conditions and concomitant complications, including lower limb ischemia.

2. Patients and methods

We retrospectively reviewed the medical records of all the patients admitted in our ICU over an 8-year period with the diagnosis of HHNS. Due to the absence of any currently definite consensus on the definition of HHNS [2], we used the association of following inclusion criteria: 1) a calculated serum osmolarity > 320 mOsm/l using the following equation: Serum osmolarity = 2 × (Na + K) + glucose (mmol/l) + BUN (mmol/l); 2) a plasma glucose value > 16.5 mmol/l; and 3) the presence of intense dehydration with impaired consciousness (stupor or coma). Because overlap exists with diabetic ketoacidosis [3,15], patients presenting with both elevated osmolarity and significant urinary ketones were excluded. Patients were treated according to the standard clinical practice at the discretion of the attending physicians. On admission, we collected the following data: age, sex, history of diabetes mellitus, underlying medical conditions, core temperature, systolic and diastolic blood pressure, heart rate, Glasgow Coma score, calculated serum osmolarity, blood glucose concentration, serum sodium concentration, serum creatinine concentration, serum protein concentration, blood urea nitrogen (BUN), white blood cell count, hemoglobin, blood C reactive protein level, lipase, arterial pH, PaO2/FiO2 ratio, and glycazed haemoglobin. Corrected serum sodium concentration was calculated using the following formula: sodium (mmol/l) + 1.65 × (glucose (mg/dl) – 100)/100 [16]. Physiologic variables measured at admission were used to calculate the simplified acute physiology score (SAPS) II [17]. The presence of lower limb ischemia at any time during ICU hospitalization and the outcome at ICU discharge were recorded. All recorded variables were analyzed to identify possible correlations with the patient outcome and the presence of lower limb ischemia. Long-term survival was determined by phoning the patient if alive, his next of kin or his treating physician, provided with information regarding the purposes of this study.

3. Statistical analysis

Results are presented as median [25–75% percentiles]. Comparisons were performed using Mann–Whitney U-tests for continuous variables or Fischer’s exact tests for categorical variables. Significance level was set at P ≤ 0.05. Statistical software (Staview®, SAS Institute Inc., North Carolina, USA) was used for our data analysis.

4. Results

From January 1998 to December 2005, 17 consecutive patients (9F/8M, age: 75 years [57–81], SAPS II: 51 [39–61]) were admitted in our ICU for HHNS. Among these patients, 76% demonstrated limited autonomy (with a certain degree of dependence for food intake and hydration) and 53% lived alone. Underlying morbidities included: hypertension (12/17 cases), past history of diabetes mellitus (7/17), neuro-psychiatric impairments (5/17), chronic renal insufficiency...
Table 1
Biological parameters on ICU admission of 17 patients with a severe diabetic non-ketotic hyperosmolar syndrome with comparisons according to the presence or not of acute lower limb ischemia (significance level: \( P \leq 0.05 \))

<table>
<thead>
<tr>
<th>Parameters (^a)</th>
<th>Total population ((N = 17))</th>
<th>With lower limb ischemia ((N = 4))</th>
<th>Without lower limb ischemia ((N = 13))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose concentration (mmol/l)</td>
<td>40.0 [26.3–60.8]</td>
<td>32.3 [29.1–34.9]</td>
<td>47.4 [24.4–62.8]</td>
<td>NS</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>33.4 [24.9–79]</td>
<td>48.8 [37.3–63.7]</td>
<td>31.5 [21.7–37.2]</td>
<td>0.03</td>
</tr>
<tr>
<td>Lipase (IU/l)</td>
<td>15.0 [10.6–18.3]</td>
<td>21.6 [17.4–23.7]</td>
<td>12.3 [9.9–16.3]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

\(^a\) Parameters are expressed as median [25–75% percentiles].

(2/17), peripheral occlusive vascular disease (1/17), thyroid cancer (1/17), and heart failure (1/17).

Vital signs on admission included Glasgow Coma score 13 [12–14], systolic blood pressure 115 mmHg [90–133], diastolic blood pressure 67 mmHg [49–79], heart rate 103 per min [89–112], and core temperature 36.7 °C [36.1–37.8]. All patients demonstrated serious metabolic disturbances with severe dehydration and acute renal failure (Table 1). An infection was identified as a precipitating factor for the onset of diabetic hyperosmolarity in 47% of the patients, including seven community-acquired pneumonia and one Escherichia coli bacteriemic urinrary-tract infection. Other precipitating factors included: undiagnosed diabetes (10/17 cases), anorexia (7/17), due to coexisting diseases, oral candidosis-associated fluid swallowing disorders, and prolonged fasting for religious purposes, corticoid administration (1/17), and non-compliance (1/17). All patients were adequately rehydrated and received intravenous insulin therapy. Eight patients received empiric broad-spectrum antibiotics pending the results of cultures. Four patients were mechanically ventilated, two received catecholamines, and one received hemodialysis. Duration of ICU stay was 5 days [3–7]. Three out of the 17 patients (18%) died in the ICU. Causes of death were stroke, septic shock, and multiorgan failure. Non-survivors were significantly older than patients who survived (88 years [84–98] versus 64 years [56–78], \( P = 0.02 \)). Using univariate analysis, no other parameter measured on admission was related to ICU mortality. Duration of hospitalization was 23 days [8–49]. Long-term (6 years [4–8]) follow-up showed a 41% survival rate and significant disabilities in survivors.

Four patients (24%) presented with acute lower limb ischemia on ICU admission. These patients had significantly more elevated BUN \(( P = 0.03 \)), creatinine phosphokinase activity \(( P = 0.04 \)), and white blood cell count \(( P = 0.02 \) (Table 1). Among these four patients, only one died. This 82-year-old female patient suffered from previous hemiplegia and peripheral occlusive vascular disease. She presented with arterial thromboembolic occlusion of the right leg with no perceptible pedial and tibial pulses. She died on day 3 due to multiorgan failure. In the three surviving patients, ischemia involved both distal extremities. All peripheral lower limb pulses were symmetrical on admission. Doppler and angiographic findings excluded arterial obstruction. Only standard medical care, including antiseptics and dressings, was needed. No one required surgical treatment. Lower limb cyanosis resolved with fluid loading and resulted in toe dry digital necrosis (Fig. 1). The factors associated with the onset of this complication were severe dehydration (likely leading to more severe hyperviscosity reflected by marked hyperosmolarity) \(( P = 0.08 \)), catecholamine-treated shock (two cases), and identification of cholesterol embolism on skin biopsy (one case).

5. Discussion

As previously reported [4–11], our series confirmed the poor short and long-term prognosis of life-threatening HHNS patients admitted in ICU. Our observational study also clearly established that acute lower limb ischemia is a frequent feature encountered in this setting.

Diabetes was undiagnosed in the majority of our patients, reflecting the problem that early symptoms of the disease are often difficult to recognize and explaining the admissions with life-threatening HHNS-related impairments. Glucosuric diuresis is the initiating event in HHNS, impairing the concentrating capacity of kidneys and further exacerbating water loss [13, 14]. Water compensation becomes rapidly inadequate in aged or severely disabled patients. Loss of more water than sodium leads to hyperosmolality. In parallel, the decreased vascular volume or the underlying renal disease alters the glomerular filtration, causing an increased glucose level. Insulin is present, but not adequate to reduce blood glucose levels, particularly when significant insulin resistance is present, like in cases of systemic infection, which was the leading cause of HHNS in our series.
HHNS is characterized by very elevated serum osmolarity and severe dehydration [13,14]. We clearly believe that these impairments represent the cornerstone mechanism of the observed acute lower limb ischemia. Indeed, the bilateral, symmetrical, and distal extremity involvement noted in three of our patients was likely to be caused by the combination of hyperviscosity and diminished blood flow due to hypotension, vasoconstrictors, or cholesterol emboli. Although worsened by some degrees of pre-existing peripheral occlusive vascular disease, isolated toe ischemia as well as Doppler and angiographic patterns, clearly refuted a proximal arterial thromboembolic complication, as is usually reported in HHNS. Moreover, numerous data show evidence for impaired haemorheological characteristics in diabetes mellitus, facilitating distal extremities ischemia. Diabetic patients, especially those with hypoxia or ischemia, exhibit aggravated haemorheological disturbances including increased blood viscosity at low shear rate, erythrocyte hyperaggregation, increased fibrinogen level, and decreased albumin level [18]. Moreover, local skin infection could also enhance injuries.

Several limitations exist in our study. We present HHNS outcomes in only one center. The number of patients may have been insufficient to yield any persuasive statistically significant findings. Otherwise, we are aware of a possible selection bias regarding the high number of patients with undiagnosed diabetes due to the low socio-economic condition of the population referred to our center.

In conclusion, HHNS is a rare but life-threatening cause of diabetic patient admission to the ICU. There is an increased incidence of lower limb ischemia in HHNS patients, possibly caused by severe dehydration and hyperviscosity. Physicians should be aware of such complications when considering fluid deficit correction, optimal monitoring, and therapeutic decisions.

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References
