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Febrile rhabdomyolysis of unknown origin in refugees coming from West Africa through the Mediterranean

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ABSTRACT

Objectives: Cases of undiagnosed severe febrile rhabdomyolysis in refugees coming from West Africa, mainly from Nigeria, has been observed since May 2014. The aim of this study was to describe this phenomenon.
Methods: This was a multicentre retrospective observational study of cases of febrile rhabdomyolysis reported from May 2014 to December 2016 in 12 Italian centres.
Results: A total of 48 cases were observed, mainly in young males. The mean time interval between the day of departure from Libya and symptom onset was 26.2 days. An average 8.3 further days elapsed before medical care was sought. All patients were hospitalized with fever and very intense muscle aches. Creatine phosphokinase, aspartate aminotransferase, and lactate dehydrogenase values were abnormal in all cases. The rhabdomyolysis was ascribed to an infective agent in 16 (33.3%) cases. In the remaining cases, the aetiology was undefined. Four out of seven patients tested had sickle cell trait. No alcohol abuse or drug intake was reported, apart from a single reported case of khat ingestion.
Conclusions: The long incubation period does not support a mechanical cause of rhabdomyolysis. Furthermore, viral infections such as those caused by coxsackievirus are rarely associated with such a severe clinical presentation. It is hypothesized that other predisposing conditions like genetic factors, unknown infections, or unreported non-conventional remedies may be involved. Targeted surveillance of rhabdomyolysis cases is warranted.

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Introduction

Rhabdomyolysis is a complex medical condition involving the rapid breakdown of damaged skeletal muscle. The severity of the illness ranges from asymptomatic elevations of serum creatine phosphokinase (CPK) to life-threatening diseases such as cardiac arrhythmia, acute renal failure, and even death. The characteristic triad of complaints, i.e. muscle pain, weakness, and pigmenturia, is seen in less than 10% of patients (Zutt et al., 2014).

According to the International Organization for Migration, 153 842 people arrived directly in Italy via the sea in 2015 and 181 436 people in 2016, mainly coming from Nigeria, Eritrea, Guinea, Ivory Coast, Gambia, Senegal, Mali, and Sudan (International Organization for Migration, 2017). An increasing number of cases of febrile rhabdomyolysis have been observed in these migrants since May 2014, and so far there has been no specific aetiological diagnosis. The aim of this study was to report and describe this phenomenon.

Materials and methods

This was a multicentre retrospective observational study of cases of febrile rhabdomyolysis reported from May 2014 to December 2016 in 12 Italian centres: nine infectious diseases and tropical medicine units, two internal medicine units, and one refugee centre (Figure 1).

Febrile rhabdomyolysis was defined as an increase in CPK levels ($\geq$1000 IU/l) associated with myalgia and fever (>38 °C). Patient demographic, clinical, and travel-related data were collected using a standardized anonymous questionnaire and were entered into a database. Data were collected retrospectively and analysed using Microsoft Office Excel 2010 (Microsoft Inc., Redmond, WA, USA). Categorical variables were expressed as the number and proportion, and continuous variables were expressed as the mean ± standard deviation (SD). The study was conducted under the provisions of the Declaration of Helsinki and in accordance with the International Conference on Harmonization Consolidated Guideline on Good Clinical Practice. Since this study was retrospective and non-pharmacological, written informed consent was not provided. In Italy, ethical authorization for these studies is not required (see Italian guidelines for the classification and conduct of observational studies, established by the Italian Drug Agency, "Agenzia Italiana del Farmaco-AIFA" on March 20, 2008).

Results

A total of 48 cases were identified; 43 were male (89.6%), and their mean age was 22.4 ± 5.8 years. They all came from West Africa, mainly from Nigeria (58.3%) (Figure 2). Libya was the departure port in all cases. After their arrival in Italy, all patients were hosted in specific shelter centres, according to Italian immigration policies. The mean time interval between the day of departure from Libya and symptom onset was 26.2 ± 39.5 days (range 2–252 days), and an average further 8.3 ± 7.85 days elapsed before medical care was sought. The mean duration of sea travel was 1.7 ± 1.26 days.

Twenty-two patients (45.8%) had travelled between September and April and 20 had travelled between May and August (this information was not available for six patients). All patients had a fever and very intense muscle aches, and were unable to stand or walk. CPK, aspartate aminotransferase, and lactate dehydrogenase values were abnormal in all cases (Table 1). Seventeen patients (35.4%) reported having a forced position during travel. No seawater ingestion was reported and no case of hypernatraemia was identified: the mean serum sodium value was 137 ± 1.26 mmol/l.

The rhabdomyolysis was ascribed by the treating physicians to an infective agent in 16 (33.3%) cases. In detail, Epstein–Barr virus (EBV) DNA was detected in eight of 32 patients tested, IgM for coxsackievirus was detected in five of 27 cases tested, and IgM for cytomegalovirus was identified in three of 29 cases tested (Table 2). The aetiology was undefined in the remaining cases. The most frequent infectious causes of rhabdomyolysis were excluded. Four out of seven patients who were tested for abnormal haemoglobin had sickle cell trait (SCT) and one patient had haemophilia A.

All patients were asked about drug and alcohol abuse, but none reported either, with the exception of one patient who declared *Catha edulis* (khat) consumption during his stay in Libya, 2–3 weeks before symptom onset.

Only one patient was treated with rifampicin, isoniazid, and pyridoxine before symptom occurrence. Following supportive treatment with hydration, almost all patients recovered completely in about a week. However, they were often symptomatic for months. Two were hospitalized in the intensive care unit and one patient had acute kidney injury.

Discussion

This study describes 48 cases of rhabdomyolysis in refugees coming from West Africa. The phenomenon caught the authors' attention because of the severity of the symptoms, the inability to obtain a definitive diagnosis, and the consistent number of cases. Cases were observed in centres distributed throughout Italy, from the north to the south. Up to 20% of individuals in the general population have an asymptomatic increase in serum CPK, and this particularly affects the black race (Gabow et al., 1982). Nevertheless, the presence of severe symptoms and fever, as well as the young age of the present study cases, prompted further investigations to determine an aetiological cause.

Many causes of rhabdomyolysis have been identified and reported in the literature, and these can be categorized into acquired and inherited causes (Gabow et al., 1982; Huerta-Alardin

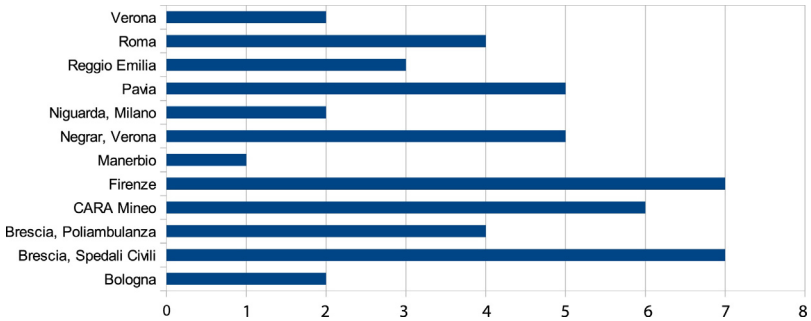

Figure 1. Number of cases reported from each Italian Centre.

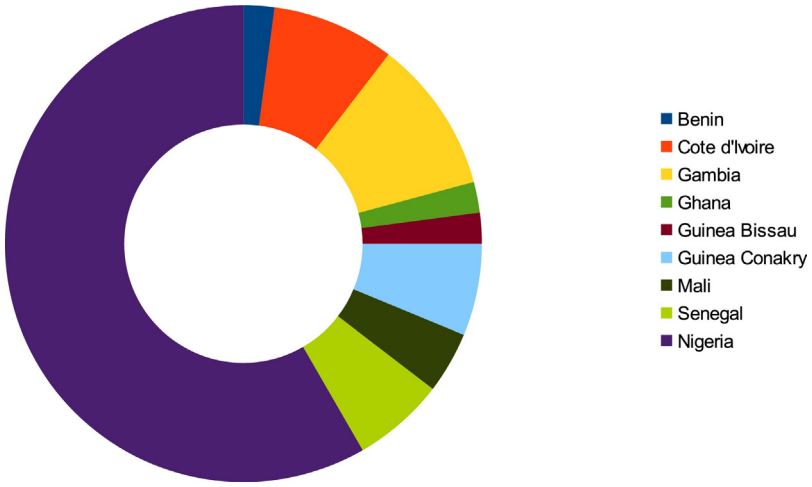

Figure 2. Country of residence of refugees.

et al., 2005; Melli et al., 2005; Zutt et al., 2014). With regard to a possible infectious aetiology, EBV has been associated with the development of rhabdomyolysis, but only rarely (Roychowdhury, 2007), and a wide spectrum of muscle disorders caused by coxsackievirus B, ranging from acute non-specific myalgia to rhabdomyolysis, has been described (Fodili and van Bommel, 2003; Gómez et al., 2008; Marinella, 1998; Wang et al., 2006).

A mechanical cause of rhabdomyolysis should also be considered. However, the long incubation period is not consistent with this hypothesis. It is known that CPK increases approximately 2–12 h after the onset of muscle injury, reaching a peak concentration after 24–72 h (Zutt et al., 2014). In the cases in this study, the mean time interval between travel and symptom occurrence was 26.2 ± 39.5 days. In more detail, the symptoms occurred about 2 months after arrival in three cases, and in one case 252 days elapsed between arrival and the clinic visit date.

It could be hypothesized that a common viral infection, like coxsackievirus B, could have triggered the rhabdomyolysis because of underlying muscle damage due to the patient's forced position during travel. Otherwise viral infections caused by EBV and coxsackievirus are only rarely associated with such a severe clinical presentation. Furthermore, in the authors' experience, serological tests were positive only in a minority of cases (25% and 18.5% of cases, respectively). The ingestion of sea water has recently been reported as a cause of hypernatremia and rhabdomyolysis in African migrants arriving in Lampedusa through the Strait of Sicily (Pasta and Mesa Suero, 2012). Nevertheless, no cases of sea water ingestion were reported in the study population and their electrolyte balance was always normal.

Table 1
Laboratory tests at presentation (mean ± standard deviation values).

WBC ($\times 10^9$/l) (n = 48/48)	5.87 ± 3.1
RBC ($\times 10^9$/l) (n = 48/48)	4.78 ± 5.59
Hb (g/dl) (n = 48/48)	13.2 ± 1.61
PLT ($\times 10^9$/l) (n = 46/48)	156 ± 46.4
AST (U/l) (n = 47/48)	355.8 ± 240.1
ALT (U/l) (n = 48/48)	142.2 ± 158.2
GGT (U/l) (n = 37/48)	50.9 ± 47.6
CPK (U/l) (n = 48/48)	8422.2 ± 6630.8
Creatinine (mg/dl) (n = 35/48)	0.98 ± 0.41
LDH (U/l) (n = 32/48)	722.8 ± 399.04
Myoglobin (ng/ml) (n = 14/48)	2088.9 ± 1299.0
CRP (mg/l) (n = 14/48)	33.9 ± 38.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; Hb, haemoglobin; LDH, lactate dehydrogenase; PLT, platelet count; RBC, red blood cell count; WBC, white blood cell count.

All patients were asked about drug or alcohol abuse, but none reported this except for one patient who declared *Catha edulis* (khat) consumption during his stay in Libya, 2–3 weeks before symptom onset. Khat is a flowering plant native to the Horn of Africa and the Arabian Peninsula, classified by the World Health Organization as a drug of abuse. It is used as a stimulant for its amphetamine-like effect, causing excitement, loss of appetite, and euphoria. This risk factor must be further addressed in a prospective manner in the future, as patients may be reluctant to disclose the intake or abuse of illicit herbs or drugs.

Different genetic defects causing various neuromuscular and metabolic disorders are known to be associated with rhabdomyolysis. In some instances, rhabdomyolysis may be due to a combination of environmental triggering causes combined with predisposing genetic factors that may well be overlooked. Therefore, the risk of recurrence is high if the genetic diagnosis is not considered (Scalco et al., 2015).

The common geographic area of origin suggests a genetic predisposition to rhabdomyolysis. Many genetic variants have been described associated with rhabdomyolysis secondary to trauma, strenuous exercise, specific drugs, and myopathies. Of note, several case reports published since the early 1970s have described significant morbidity and mortality of acute exertional rhabdomyolysis in patients with SCT. A case of severe exertional rhabdomyolysis after a 1.5 mile run was reported in a 27-year-old medical doctor who had a past medical history significant only for SCT (Makaryus et al., 2007). In the present study sample, four out of seven patients screened for SCT were positive. Despite the small sample, it may be worth looking for this and possibly other genetic predisposing factors that may be common to refugees coming from West Africa.

Other haematological disorders and haemoglobinopathies have been recognized as associated with rhabdomyolysis, such as glucose-6-phosphate dehydrogenase (G6PDH) deficiency (Mangat et al., 2014) and thalassemia (Niwa et al., 1979), especially in situations of stress, after exposure to a strong oxidant, food items, or medicines, or drug intake.

Another recent report observed a significant difference in coenzyme Q10 (CoQ10) between healthy African Americans and whites, indicating that higher creatine phosphokinase (CPK) and lower CoQ10 are associated with severe exertional rhabdomyolysis only in African Americans. The CK to CoQ10 ratio is even more

Table 2
Diagnostic tests.

Pathogen	Laboratory evidence of recent or chronic active infection[a],*n*/*N* (%)	Laboratory evidence of non-immunity, *n*/*N* (%) where appropriate
Adenovirus	0/15 (0)	10/15 (66.6)
CMV	3[a]/29 (10.3)	3/29 (10.3)
Coxsackievirus	5[a]/27 (18.5)	0/27 (0)
EBV	8[b]/32 (25)	21/32 (65.6)
Plasmodium falciparum	1[c]/44 (2.27)	–
Dengue	0/17 (0)	13/17 (76.4)
Schistosoma	3[d]/10 (30)	–
Chikungunya	2[e]/10 (20)	–
HCV	0/35 (0)	–
HBV	3/38 (7.9)	–
HIV	2/39 (5.1)	–

n, number of patients tested; *N*, number of patients with available data; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus.
[a] IgG and IgM positive or documented seroconversion (from negative to positive IgG).
[b] Eight patients with positive EBV DNA.
[c] Thin and thick blood smear positive.
[d] Three patients with Schistosoma IgG positive (probable chronic infection).
[e] Two patients positive for both chikungunya IgG and IgM.

specific. However, possible additional exertional rhabdomyolysis risk factors and multiple required deficiencies in the same individual must be considered (Prince et al., 2015).

An outbreak of Haff disease has been described recently in Salvador, Brazil, starting early December 2016, and several cases have occurred in recent years in Eastern Europe, Sweden, China, Japan, and the USA (Bandeira et al., 2017; Diaz, 2015). Haff disease is a syndrome of myalgia and rhabdomyolysis that occurs within 24 h after consuming cooked seafood; it is caused by an as yet unidentified heat-stable toxin. No data about the ingestion of fish were collected from the present study patients, but Haff disease was excluded from the physicians' working diagnosis due to the presence of fever (which has not been described in Haff disease), the heterogeneous incubation period, and the distribution throughout the country. Furthermore, no cases have been reported in the literature in Italian people, and this allowed the possibility of a disease related to the consumption of Italian fish being ruled out.

This study has several limitations. Data were not collected systematically in all infectious diseases units of the country, so they may not be representative of all migrants with rhabdomyolysis. This was not a population-based study, so rates and risks could not be determined. The data collection system changed with time. The progressive increase in the number of cases observed may have been due in part to a raised awareness. Moreover, the medical records were not always homogeneous. Despite these limitations, this study provides the best current estimates available on rhabdomyolysis in refugees.

In conclusion, rhabdomyolysis is a potentially serious clinical illness. The consistent number of cases observed served as a wake-up call and prompted the authors to wonder whether something unusual and unexpected was occurring. Genetic predisposing factors must be considered and studied, and a full analysis for haemoglobinopathies and G6PDH deficiency should be performed. A detailed history of drug/herbal intake is also essential. Additionally, a more uniform and organized data collection system for these patients is necessary in order to better understand the phenomenon. Targeted surveillance of rhabdomyolysis cases is warranted.

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Conflict of interest

All authors declare no conflicts of interest.

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