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

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Highlights

- Rhabdomyolysis is a complex medical condition involving the rapid dissolution of damaged skeletal muscle;
- We are observing an increasing number of cases of febrile rhabdomyolysis migrants coming from West Africa via the sea;
- We are not able to identify a specific aetiologic diagnosis of rhabdomyolysis;
- Genetic predisposing factors favouring clinical manifestations, unknown infections or unreported non conventional remedies may be involved;
- Targeted surveillance of rhabdomyolysis cases is warranted.

Abstract

Objectives: Since May 2014 we are observing cases of undiagnosed severe febrile rhabdomyolysis in refugees coming from West Africa, mainly from Nigeria. Aim of this study is to describe this phenomenon.

Methods: A multicenter retrospective observational study of cases of febrile rhabdomyolysis reported from May 2014 to December 2016 in 12 Italian Centers.

Results: A total of 48 cases were observed, mainly young males. Mean time between the date of departure from Lybia and symptoms onset was 26.2 days. An average of further 8.3 days elapsed before medical case was searched. All patients were hospitalized with fever and very intense muscle aches. CPK, aspartate aminotransferase (AST), lactate dehydrogenase (LDH) values were always abnormal. 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 signs of alcohol abuse or drugs intake were reported, apart from a single reported case of khat ingestion.

Conclusions: The long incubation period doesn't support a mechanical cause of rhabdomyolysis. Otherwise, viral infections like Coxsackie virus are hardly associated with such severe clinical presentation. We hypothesize that other predisposing conditions like genetic factors, unknown infections or unreported non conventional remedies may be involved. Targeted surveillance of rhabdomyolysis cases is warranted.

Keywords: refugees, West Africa, Nigeria, rhabdomyolysis, fever, creatinekinase

Background: Rhabdomyolysis is a complex medical condition involving the rapid dissolution of damaged skeletal muscle. The severity of illness ranges from asymptomatic elevations of serum creatinekinase (CPK) to life-threatening diseases such as cardiac arrhythmia, acute renal failure and even death. The characteristic triad of complaints, 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 and 181.436 people arrived directly in Italy via the sea in 2015 and 2016

respectively, mainly coming from Nigeria, Eritrea, Guinea, Ivory Coast, Gambia, Senegal, Mali and Sudan [International Organization for Migration, 2017]. Since May 2014 we are observing an increasing number of cases of febrile rhabdomyolysis in these migrants, so far without any specific aetiologic diagnosis. Aim of this study is to report and describe this phenomenon.

Material/methods: A multicenter retrospective observational study of cases of febrile rhabdomyolysis reported from May 2014 to December 2016 in 12 Italian Centers: 9 Infectious Diseases and Tropical Medicine Units, 2 Internal Medicine Units and 1 Refugee Centre (Figure 1). Febrile rhabdomyolysis is defined as an increase in CPK levels (≥1000 UI/L) associated with myalgia and fever (>38°C). Patients' demographical, clinical and travel-related data were collected according to a standardized anonymous questionnaire and entered into a database. Data were retrospectively collected and analysed with Microsoft Office Excel® (2010, Microsoft INC, Redmont, USA). Categorical variables are expressed as numbers and proportions, continuous variables are expressed as 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, a written informed consent was not provided. In Italy, ethical authorization for these studies is not required (see Italian Guidelines for classification and conduction of observational studies, established by the Italian Drug Agency, "Agenzia Italiana del Farmaco-AIFA" on March 20th, 2008).

Results: A total of 48 cases were observed: 43 were males (89.6%), mean age was 22.4 years (± 5.8). 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 centers, according to Italian immigration policies. The mean time between the date of departure from Lybia and symptoms onset was 26.2 days (±39.5; min 2 -max 252 days) and an average of further 8.3 days (± 7.85) elapsed before medical care was searched. Sea-travel mean duration was 1.7 days (±1.26). Twenty-two patients (45.8%) had travelled from September to April and other

twenty from May to August (for 6 patients this detail was not available). All patients had fever and very intense muscle aches with inability to stand and walk. CPK, aspartate aminotransferase (AST), lactate dehydrogenase (LDH) values were always abnormal (Table 1). Seventeen patients (35.4%) reported having a forced position during travel. No seawater ingestion was reported and no cases of hypernatraemia were identified: mean value of serum sodium: 137 mmoL/L(±1.26).

Rhabdomyolysis was ascribed by the treating physicians to an infective agent in 16 (33.3%) cases. In detail, EBV-DNA was detected in 8 of 32 patients that were tested, IgM for Coxsackie virus were detected in 5 of 27 and IgM for Cytomegalovirus in 3 of 29 (Table 2). In the remaining cases the aetiology was undefined. The most frequent infectious causes of rhabdomyolysis were excluded. Four out of seven patients who were tested for abnormal haemoglobins had sickle cell trait and one patient had haemophilia A.

All patients were asked about drugs or alcohol abuse but no cases were reported except one patient who declared Cahta edulis (kaht) consumption during his stay in Lybia, 2-3 weeks before symptoms onset. Only one patient was treated with rifampicin, isoniazid and pyridoxine before symptoms occurrence. Almost all patients recovered completely in about a week after supportive treatment with hydration but they were often symptomatic for months. Two were hospitalized in intensive care unit and one patient had acute kidney injury.

Discussion: The study describes 48 cases of rhabomyolysis in refugees coming from West Africa. The phenomenon has caught our attentions because of the severity of symptoms, the inability to obtain a definitive diagnosis and the consistent number of cases. Cases were observed in Centers distributed throughout Italy, from North to South. In general population, up to 20% of individuals have asymptomatic increase of serum creatinekinase, especially in the Black race [Gabow et al., 1982]. Anyway, the presence in our cases of severe symptoms, fever and the young age should prompt to perform further investigation in order to define an aetiologic cause. In literature, many causes of rhabdomyolysis have been identified and can be categorised into acquired and inherited causes [Gabow et al, 1982; Huerta-Alardin et al., 2005; Melli et al, 2005; Zutt et al, 2014]. Taking

into consideration infectious aetiology, Epstein-Barr Virus (EBV) has rarely been associated with development of rhabdomyolysis [Roychowdhury, 2007], but a wide spectrum of muscle disorders caused by Coxsackie B virus, ranging from acute non-specific myalgia to rhabdomyolysis, have been described [Fodili and van Bommel, 2003; Gomez et al., 2008; Marinella, 1998; Wang et al., 2006]. Mechanical cause of rhabdomyolysis must be considered. However, the long incubation period is not consistent with this hypothesis. It is known that approximately 2-12 h after the onset of muscle injury CPK increases, reaching the peak concentration after 24-72 hours [Zutt et al., 2014]. In our cases, mean time between travel and symptoms occurrence was 26.2 days (±39.5). In more detail, in three cases the symptoms occurred about 2 months after arrival and in one case 252 days elapsed between arrival and clinic visit date. We can hypothesize that a common viral infection, like Coxsackie B virus, may trigger rhabdomyolysis because of underlying muscle damage due to forced position taken during travel. Otherwise viral infections like Epstein-Barr or Coxsackie virus are hardly associated with such severe clinical presentation, and in our experience serological test were positive only in a minority of cases (respectively 25% and 18.5% of cases). Ingestion of sea water has recently been reported as 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 have been reported in our study and electrolytic balance was always normal.

All patients were asked about drugs or alcohol abuse but no cases were reported except one patient who declared Cahta edulis (kaht) consumption during his stay in Lybia, 2-3 weeks before symptoms onset. Kaht is a flowering plant native to the Horn of Africa and the Arabian Peninsula, classified by WHO as a drug of abuse. It is used as 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 reticent to disclose the intake of abuse 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 superimposed on predisposing genetic factors that may well remain unappreciated. Therefore, the risk of recurrence is high if the genetic diagnosis is not considered (Scalco et al., 2015).

The common geographic area of origin suggest a genetic predisposition to rhabdomyolysis. Many genetics variants have been described associated to rhabdomyolysis secondary to trauma, strenuous exercise, specific drugs and myopathies. Of note, several case reports published since the early 1970s described significant morbidity and mortality of acute exertional rhabdomyolysis in patients with sickle cell trait (SCT). A case of severe exertional rhabdomyolysis has been reported in a 27-year-old medical doctor after a 1.5 mile run and a past medical history significant only for SCT [Makaryus et al., 2007]. In our study, 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 haematologic disorders and haemoglobinopaties have been recognised as associated with rhabdomyolysis such as glucose 6 phosphate dehydrogenase (G6PD) deficiency [Mangat C et al., 2014] and thalassemia [Niwa T et al., 1979], especially in stress situations, after exposure to a strong oxidant, food items or medicines, or drugs intake.

Another recent report observed a significant difference in Coenzyme Q10 (CoQ10) between healthy African American and whites, indicating that higher CK and lower CoQ10 are associated with severe exertional rhabdomyolysis only in African Americans. The CK:CoQ10 ratio is even more 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 diseases has been recently described in Salvador, Brazil, starting early December 2016 and several cases occured in recent years in Eastern Europe, Sweden, China, Japan and United States (Bandeira et al., 2017; Diaz JH, 2015). Haff disease is a syndrome of myalgia and rhabdomyolysis that occurs within 24 h after consuming cooked seafood, an it is caused by a yet

unidentified heat-stable toxin. No data about ingestion of fish was collected in our patients, but Haff disease have been excluded in physicians' working diagnosis due to the presence of fever, not described in Haff disease, the heterogeneous incubation period and the distribution throughout the Country. Furthermore, no cases have been reported in literature in Italian people and this allows us to rule out the possibility of a disease related to consumption of Italian fish.

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

Conclusions: Rhabdomyolysis is a potentially serious clinical illness. The consistent number of cases observed served as wake-up call and prompted us to wonder whether we were looking at something unusual and unexpected. Genetic predisposing factors must be considered and studied, and full analysis for haemoglobinopathies and G6PDH deficiency should be performed. A detailed history of drugs/herbal intake is also mandatory. Additionaly, a more uniform and organized data collection system for these patients is mandatory in order to better understand the phenomenon. A targeted surveillance of rhabdomyolysis cases is warranted.

Conflicts of interest: All the authors declare no conflicts of interest.

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

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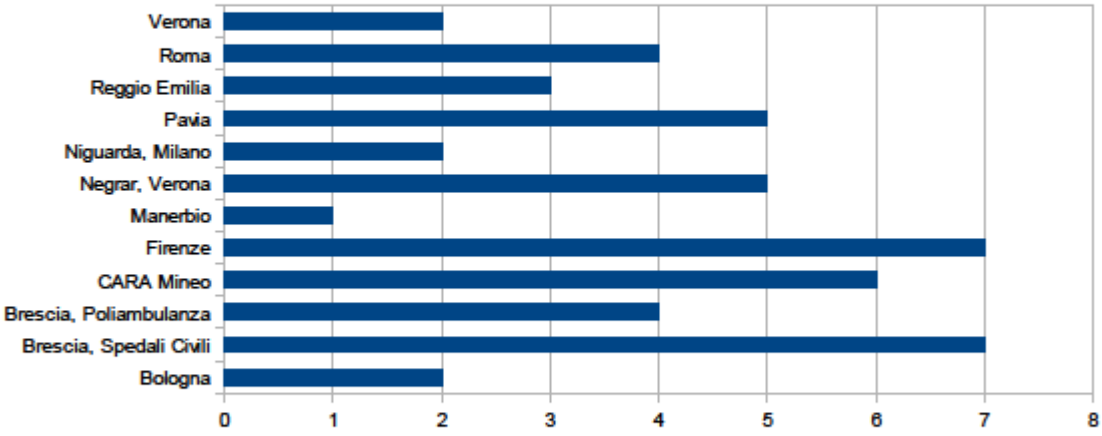

Figure 2. Country of residence of refugees

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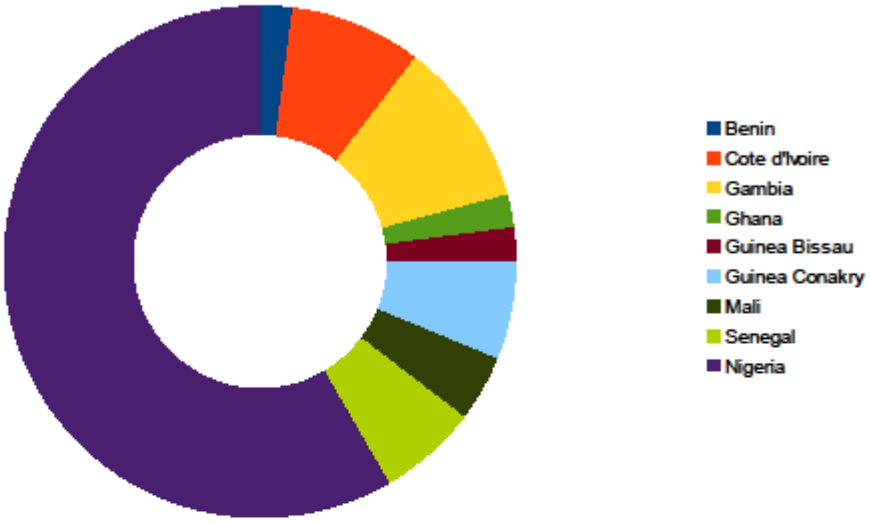

Table 1. Laboratory tests at onset (mean values ± SD)

WBC [x10^3/microL] (n=48/48)	5.87 (±3.1)
RBC [x10^3/microL] (n=48/48)	4.78 (±5.59)
Hb [g/dl] (n=48/48)	13.2 (±1.61)
PLT [x10^3/microL] (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)**
CREAT [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)**
C-Reactive Proteine [mg/L](CRP) (n=14/48)	**33.9 (±38.2)**

Table 2. Diagnostic tests

Pathogen	Laboratory evidence of recent or chronic active infection* (n/N; %)	Laboratory evidence of non immunity (n/N; %) (where appropriate)
Adenovirus	0/15; 0	10/15; 66.6
CMV	3*/29; 10.3	3/29; 10.3
Coxsackie	5*/27; 18.5	0/27; 0
EBV	8^/32; 25	21/32; 65.6
Plasmodium falciparum	1°/44; 2.27	--
Dengue	0/17; 0	13/17; 76.4
Schistosoma	3£/10; 30	--
Chikungunya	2§/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

*IgG and IgM positive or documented seroconversion (from negative to positive IgG)

^8 patients with positive EBV-DNA

°Thin and thick blood smear positive

£ 3 patients with Schistosoma IgG positive (probable chronic infection)

§ 2 patients with both Chikungunya IgG and IgM positive