CASE REPORT

Illegal immigration: the puzzling role of several risk factors for rhabdomyolysis

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SUMMARY

A 14-year-old boy presented with low-grade fever, widespread myalgia and difficulty in walking and standing 2 days after the undocumented trip which brought him from western Africa to Italy. His serum creatine phosphokinase was markedly elevated. He was diagnosed with rhabdomyolysis and was volume-restored with normal saline and bicarbonate-containing fluid. Anamnesis revealed illegal, not well-specified, forced consumption in his fatherland, and very bad conditions of the trip (prolonged immobility, dehydration, hypothermia). Workup included a respiratory microbiological panel which was positive for *Chlamydia pneumoniae*. Other microbiological agents were excluded. After 3 weeks, he recovered complete motility. Undocumented immigrants may present several risk factors for rhabdomyolysis that give to this group of individuals a higher risk of developing this disorder.

CASE PRESENTATION

Our patient is a 14-year-old boy coming from Gambia (western Africa) with a landing of 943 immigrants. After 3 days from his arrival in Italy, he had low-grade fever (37.5°C) and widespread myalgia with difficulty in walking and sustaining his weight in order to stand upright. He was therefore led to the emergency room and then to the paediatric intensive care unit of the Messina University Hospital. There, he appeared in poor clinical condition with signs of dehydration. On examination, vital signs (oximetry, heart and breath frequency) were normal but he had low-grade fever. Physical examination of the chest and abdomen was normal; no signs of trauma in the head or in other parts of the body. Pupils were equal and showed a normal reactivity to light. Neither cranial nerve nor sensibility deficits were recorded. The deep tendon reflexes were weak. The boy showed difficulty in walking and standing upright with diffuse muscular pain. The blood examinations showed raised creatine phosphokinase (CPK) 16 000 UI/L, creatine kinase-MB (CK-MB) 312 UI/L, aspartate aminotransferase 540 UI/L, lactate dehydrogenase (LDH) 1799 UI/L and myoglobin >3940 ng/mL. Renal function and serum electrolytes were normal. Rhabdomyolysis was diagnosed. Intravenous hyperhydration therapy (ie, maintenance of fluid amount at three times the normal fluid requirements) and continuous infusion of

furosemide (0.02–0.2 mg/kg/hour, continuously calibrated to obtain the desired diuresis) were started so as to ensure urine output >200 mL/hour. Urine alkalisation with sodium bicarbonate 1 mmol/kg/day was also started. After 7 days, the patient's general clinical condition improved and muscular pain, myoglobin (1472 ng/mL) and other sarcoplasmic proteins (CPK 3803 UI/L, CK-MB 98 UI/L) serum values gradually reduced, so the boy was admitted to the paediatric ward. Here, the diuretic therapy was stopped, and the intravenous fluid intake was reduced (normal fluid requirements plus oral water intake of 1–2 L/day), with a urine output of 100–200 mL/hour. During the subsequent days, blood examinations showed a further slow reduction of all muscular proteins, with normalisation after 3 weeks. During the hospitalisation, serological analysis showed signs of acute *Chlamydia pneumoniae* infection, without respiratory symptoms. Clarithromycin therapy was started. Other Viral and bacterial (*Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*) infections were ruled out. Electromyography (EMG) performed after 2 weeks from the symptom onset was normal.

At the entrance in our ward, an anamnestic deepening revealed the extreme bad life conditions in Gambia where the boy was forced to work in the fields under the influence of no better defined drugs ('white pills', as he referred to). We could not perform blood or urine drugs and their metabolites research since a long time had passed from the last drug consumption. Besides, he referred total immobility in squatting position for 'three suns' (likely 3 days) during the boat trip.

GLOBAL HEALTH PROBLEM

- ▶ Rhabdomyolysis is a potentially life-threatening event.
- ▶ Different causes of rhabdomyolysis exist, such as drugs and toxins, traumatic events, excessive muscle activity, immobilisation, hypo- and hyperthermia, and infections.
- ▶ The elevation of CPK serum concentration is the most sensitive laboratory sign, and is enough for the diagnosis. So, urinary test and EMG are not necessary.
- ▶ Undocumented immigration is an actual phenomenon involving Italian lands, and spreading worldwide.

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- Immigrants' really poor lifestyle and the prolonged bad conditions of their trip seem to be important, often co-existent risk factors for rhabdomyolysis.

GLOBAL HEALTH PROBLEM ANALYSIS

Rhabdomyolysis is a relatively rare event with an estimated incidence of about 1–2 cases per 10 000 person-years, characterised by the breakdown of skeletal muscle cells. The consequent leakage of electrolytes and sarcoplasmic proteins from muscle cells into the circulation causes the typical blood and urine examination alterations (such as increased serum values of myoglobin, CPK, LDH, transaminases and myoglobinuria) and the potentially life-threatening complications such as electrolyte imbalance, including the particularly dangerous acute hyperkalaemia, metabolic acidosis and/or acute renal failure due to tubular injury resulting from excessive quantities of myoglobin. Three typical clinical manifestations are muscle pain, weakness and reddish-brown urine, not always present in children. The elevation of CPK serum concentration (typically >11 times the upper limit of normal) is the most sensitive laboratory sign.^{1–3} Some studies have shown higher values of serum CPK in healthy black South African subjects than in healthy Caucasian ones (only adults). A large study on 307 subjects showed that the mean total CPK level for black men was 146.5 ± 136.9 U/L (median, 108), while it was 60.8 ± 26.1 U/L (median, 51) in white men. Differences between black and white women were also reported: black women 66.4 ± 50.0 U/L (median, 53 U/L), white women 37.0 ± 18.2 U/L (median, 32).⁴ Higher median values of serum CPK (206 U/L for black men vs 142 U/L for white men) have been reported in another study.⁵ The differences in serum CPK values could have been due to greater muscle mass in black subjects compared with whites (that is the usually accepted reason for the higher CPK values in men than in women). However, the role played by not yet known genetic factors is more likely.

However, even considering average CPK values higher in the African breed than the Caucasian one, in our patient the CPK serum concentration was markedly elevated (more than 11 times the upper limit of normal), with the consequent diagnosis of rhabdomyolysis.

The most important goal of the rhabdomyolysis management is the prevention of acute renal failure by aggressive hydration at a rate of 1.5 L/hour in adults (amount at three times the normal fluid requirements), so as to ensure urine output >200 mL/hour. Continuous infusion of furosemide and urinary alkalinisation with sodium bicarbonate or sodium acetate may be used to further preserve renal function.⁶

There is a large variety of causes of rhabdomyolysis, including drugs and toxins, traumatic events, severe viral and bacterial infections, vascular alterations (such as ischaemia and heat stroke), excessive muscle activity (seizures, strenuous exercise), autoimmune inflammation (polymyositis/dermatomyositis, systemic lupus erythematosus, polyarteritis nodosa), hypothermia and hyperthermia, inborn errors of metabolism and other genetic disorders.^{1–3}

To date, the exact incidence of each cause of rhabdomyolysis is not well defined. In a recent Taiwan study on paediatric emergency patients, the leading cause of rhabdomyolysis in the age group of 0–9 years was infection, while in the age group of 10–18 years, the leading causes were trauma and exercise.¹ In adulthood, one of the most frequent causes is drug consumption. Drugs may induce rhabdomyolysis as a result of either direct toxic effect on myocyte functioning, or indirect secondary effect predisposing the myocyte to develop injury. Furthermore, drugs that induce central nervous system depression can cause

prolonged immobilisation, muscle compression and tissue ischaemia, all leading to myocyte injury.⁷

In a recent study on drug-associated rhabdomyolysis reported by the US Food and Drug Administration Adverse Event Reporting System (AERS), 8610 cases were described (higher OR for 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor-associated rhabdomyolysis) and 16 435 suspected drugs were identified in the database. Some of them are used in paediatrics such as risperidone (antipsychotic drug used in attention-deficit/hyperactivity disorders), clarithromycin, furosemide, valproate, paracetamol, omeprazole, fentanyl, metformin, ciprofloxacin, amoxicillin and insulin.³ Besides, many of the common drugs of abuse (eg, ethanol, cocaine, methamphetamine) have been reported to cause rhabdomyolysis.⁷

Regarding virus-related rhabdomyolysis, there is only a small number of reported cases including influenza, parainfluenza, echovirus, Coxsackievirus, adenovirus, Epstein-Barr virus (EBV), herpes simplex virus, HIV and Citomegalovirus (CMV). To date, the exact mechanism of virus-associated muscle destruction is still unknown. A direct viral invasion with subsequent disruption of the muscle cells appears unlikely because of the absence of demonstrable viral inclusion in affected muscles. It appears more likely an immune-mediated destructive action as a result of molecular mimicry between virus and muscle proteins.^{8–9} Less common is the bacterial infection-related rhabdomyolysis. *Legionella* spp are the most frequently involved; other bacteria include streptococci, staphylococci and Gram-negative bacteria, such as salmonella, *Mycoplasma pneumoniae*, *Neisseria meningitidis* and *Leptospira* spp. *Mycobacterium tuberculosis* rarely causes rhabdomyolysis, but may cause myositis in less than 1% of cases, spreading from a contiguous infection site (ie, an infected joint, bone, or abscess) or, less commonly, via bacteraemia.¹⁰ To our knowledge, there are no reported cases of paediatric rhabdomyolysis due to *Chlamydia pneumoniae* infection.

Finally, even some foods can cause acute rhabdomyolysis, including fish (Haff disease), wild mushrooms and quail (coturnism).¹¹

A recent article of Pasta and Mesa reports the ingestion of sea water as cause of hypernatraemia and rhabdomyolysis in African immigrants arriving in Lampedusa through the Strait of Sicily.¹²

Our patient is a 14-year-old unaccompanied immigrant from Gambia affected by rhabdomyolysis.

In 2015, 153 842 immigrants landed in Italy (vs 170 100 in 2014 and 42 925 in 2013); 16 362 of them were children (12 272 unaccompanied). Majority of them came from Eritrea (3089), Egypt (1711), Somalia (1296), Gambia (1268) and Nigeria (1006). Twelve per cent of the immigrants are actually located in Sicily. In 2015, there were 51 landings, with 9911 landed immigrants in Messina (Italy).¹³ In 2016, 181 436 people arrived directly in Italy by sea; in 2017 (updated on 30 June 2017), 83 752 arrived in Italy by sea, predominantly coming from Nigeria (14 118), Bangladesh (8241), Guinea (7759), Ivory Coast (7354) and Gambia (4920).¹⁴

Despite the difficulty of retrieving data, information coming from WHO declarations and some Italian hospitals experience show that only a small percentage of immigrants (2%–5%) arrives in Italy with a compromised health status. This is because of the 'healthy migrant effect': only healthy subjects face the journey and emigrate from the country of origin. A systematic review conducted in 2015 showed that in Europe, irregular immigrants have a lower perception of disease severity and fewer accesses to hospitals or clinics (especially pregnant women and young children). The same review showed a higher risk of traumas associated with the current and previous bad

Learning points

- ▶ Young immigrants presenting with muscle pain and weakness should undergo blood tests (creatine phosphokinase dosage) to promptly diagnose rhabdomyolysis.
- ▶ Young immigrants with rhabdomyolysis should be investigated with a thorough medical history and drug tests as soon as possible after their arrival, to highlight the use of drugs as possible cause of rhabdomyolysis. Bacteriological and viral investigations must also be carried out to rule out infectious causes.
- ▶ Border crossers seem to be a unique population, with an associated higher risk of rhabdomyolysis than the general population because of the poor living and working conditions in their fatherland, the possible use of dopes and the extreme conditions of the boat trip, characterised by prolonged immobility (often in squatting position), dehydration and exposure to either very high or very low temperatures.

living conditions. Regarding infections, epidemiological data show low percentages of immigrants suffering from infectious diseases, with a negligible risk of transmission, in the absence of specific carriers and/or socioeconomic conditions that support their diffusion. Confirmation data come from the experience of the INMP (National Institute for the Promotion of the Health of Migrant Populations and the Fight Against Related-Poverty-Diseases) outpatient clinics in Rome: from 2008 to October 2016, only 10% of the 23 025 undocumented immigrants had infectious diseases.¹⁵

The poor lifestyle in the fatherland and the bad trip condition are important risk factors for rhabdomyolysis, so immigrants are a population at high risk for the development of this condition. This situation had already been documented by Wong *et al*¹⁶ in a 2015 retrospective study of 55 immigrants from Mexico to Southwest USA. Forty-nine per cent (n=27) had an admission diagnosis of rhabdomyolysis. Urine toxicology testing was obtained from 16 patients: five were negative; six were positive for benzodiazepines, six for opiates, two for cannabinoids, two for acetone, and one for caffeine.

Our patient, and young immigrants like him, have several risk factors for rhabdomyolysis: bad lifestyle in Africa with intense physical work in the fields and forced assumption of drugs to improve the resistance to work; poor trip conditions by boat to arrive in Italy, often characterised by prolonged immobility, hypothermia and dehydration; infections. It is hard to determine which of the above-described conditions was the determining cause of rhabdomyolysis; it is likely that all of them contributed to the development of the disease.

Another case of rhabdomyolysis presented to our paediatric ward after the same landing. The second young boy reported a similar history, with the exception of drugs use; neither *Chlamydia pneumoniae* nor other infections were detected.

A recent multicentre retrospective observational study of cases of febrile rhabdomyolysis, conducted by Odolini *et al*¹⁷ between May 2014 and December 2016 in 12 Italian centres describes 48

cases, mainly young males coming from Nigeria (58.3%). Infections were diagnosed in 16 (33.3%) cases (such as EBV, CMV and Coxsackie B virus); in the remaining cases, the aetiology was undefined. Four out of seven patients tested had sickle cell trait. No signs of alcohol abuse or drug intake were reported, apart from a single reported case of khat ingestion. All patients had fever and very intense muscle aches with inability to stand and walk and 35.4% of the patients reported having a forced position during travel, like our patients.

In conclusion, border crossers may be considered a population with high risk of rhabdomyolysis; all immigrants presenting with muscle pain and weakness should be investigated for evaluation of urine (dark?) and blood tests (CPK, myoglobin) in order to rule out rhabdomyolysis.

Contributors LC conceptualised and designed the study and collected data; VD and GS carried out the initial analyses and drafted the article; CS reviewed the article and revised it critically for important intellectual content. All authors approved the final version as submitted and agree to be accountable for all aspects of the work.

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REFERENCES

- 1 Chen CY, Lin YR, Zhao LL, *et al*. Clinical spectrum of rhabdomyolysis presented to pediatric emergency department. *BMC Pediatr* 2013;13:134.
- 2 Guideline: Acute Rhabdomyolysis - Investigation and Management – CHW (Children Hospital at Westmead). 2016. Guideline No: O/C/08:8005-01:02.
- 3 Oshima Y. Characteristics of drug-associated rhabdomyolysis: analysis of 8,610 cases reported to the U.S. Food and Drug Administration. *Intern Med* 2011;50:845–53.
- 4 Black HR, Quallich H, Garelick CB. Racial differences in serum creatine kinase levels. *Am J Med* 1986;81:479–87.
- 5 Gledhill RF, Van der Merwe CA, Greyling M, *et al*. Race-gender differences in serum creatine kinase activity: a study among South Africans. *J Neurol Neurosurg Psychiatry* 1988;51:301–4.
- 6 Torres PA, Helmstetter JA, Kaye AM, *et al*. Rhabdomyolysis: pathogenesis, diagnosis, and treatment. *Ochsner J* 2015;15:58–69.
- 7 Coco TJ, Klasner AE. Drug-induced rhabdomyolysis. *Curr Opin Pediatr* 2004;16:206–10.
- 8 Hirohama D, Shimizu T, Hashimura K, *et al*. Reversible respiratory failure due to rhabdomyolysis associated with cytomegalovirus infection. *Intern Med* 2008;47:1743–6.
- 9 Tseytlin D, Maynard S. Severe rhabdomyolysis secondary to adenovirus infection: case report and literature review. *Clin Nephrol* 2016;85:245–50.
- 10 Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. *Clin Microbiol Rev* 2008;21:473–94.
- 11 Tsironi M, Andriopoulos P, Xamodrakas E, *et al*. The patient with rhabdomyolysis: have you considered quail poisoning? *CMAJ* 2004;171:325–6.
- 12 Pasta L, Mesa Suero LA. [Ingestion of sea water as cause of hypernatremia and rhabdomyolysis in African migrants arriving in Lampedusa through the Strait of Sicily]. *Epidemiol Prev* 2012;36:141.
- 13 Lunghini R. West - Welfare Società e Territorio. 2016.
- 14 International Organization for Migration. Migration flows Europe: arrivals and fatalities. 2017 http://migration.iom.int/docs/MMP/300617_Mediterranean_Update.pdf.
- 15 Baglio G, Di Palma R, Eugeni E, *et al*. [Undocumented immigrants: what do we know about their health?]. *Epidemiol Prev* 2017;41:57–63.
- 16 Wong C, Hsu W, Carr GE. Spectrum of critical illness in undocumented border crossers. The Arizona-Mexico border experience. *Ann Am Thorac Soc* 2015;12:410–4.
- 17 Odolini S, Gobbi F, Zammarchi L, *et al*. Febrile rhabdomyolysis of unknown origin in refugees coming from West Africa through the Mediterranean. *Int J Infect Dis* 2017;62:77–80.

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