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CASE REPORT

DAPSONE HYPERSENSITIVITY SYNDROME IN AN ADOLESCENT DURING TREATMENT OF LEPROSY

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SUMMARY

A 12 y old girl was admitted 24 days after start a WHO multidrug therapy scheme for multibacillary leprosy (dapsone, clofazimine and rifampicin) with intense jaundice, generalized lymphadenopathy, hepatoesplenomegaly, oral erosions, conjunctivitis, morbiliform rash and edema of face, ankles and hands. The main laboratory data on admission included: hemoglobin, 8.4 g/dL; WBC, 15,710 cells/mm^3; platelet count, 100,000 cells/mm^3; INR = 1.49; increased serum levels of aspartate and alanine aminotransferases, gamma-glutamyl transpeptidase, alkaline phosphatase, direct and indirect bilirubin. Following, the clinical conditions had deteriorated, developing exfoliative dermatitis, shock, generalized edema, acute renal and hepatic failure, pancytopenia, intestinal bleeding, pneumonia, urinary tract infection and bacteremia, needing adrenergic drugs, replacement of fluids and blood product components, and antibiotics. Ten days after admission she started to improve, and was discharged to home at day 39th, after start new supervised treatment for leprosy with clofazimine and rifampicin, without adverse effects. This presentation fulfils the criteria for the diagnosis of dapsone hypersensitivity syndrome (fever, generalized lymphadenopathy, exfoliative rash, anemia and liver involvement with mixed hepatocellular and cholestatic features). Physicians, mainly in geographical areas with high prevalence rates of leprosy, should be aware to this severe, and probably not so rare, hypersensitivity reaction to dapsone.

KEYWORDS: Dapsone syndrome; Sulfone syndrome; Hepatic failure, Leprosy.

INTRODUCTION

Dapsone has been broadly used for treatment of leprosy, a wide variety of dermatological inflammatory diseases such as dermatitis herpetiformis and chronic bullous dermatosis, *Pneumocystis carinii* and malaria prophylaxis[1,6,9-11,14-15,24-26]. Dapsone therapy may result in a variety of adverse effects, including hemolytic anemia, methemoglobinemia, hepatic involvement (hepatocellular or cholestatic disease, or both), cutaneous involvement (exanthematous eruption, Stevens-Johnson syndrome or toxic epidermal necrolysis); agranulocytosis, nephritis, pneumonitis and hypothyroidism[1,6,9,11,15-16,18]. Dapsone hypersensitivity syndrome (DHS), firstly described by ALDDAY & BARNES (1951)[1], is a severe and distinct idiosyncratic adverse reaction, with multiorgan involvement[1-5,7-8,10-14,17-25]. The present report describes a near fatal case of DHS in an adolescent.

CASE REPORT

A 12 y old girl was admitted 24 days after start a WHO multidrug therapy scheme (MDT; dapsone, clofazimine and rifampicin) for multibacillary leprosy. She was in a satisfactory health condition until six days before, when fever, malaise, headache and rash developed. After three days, were noted dark urine and jaundice, and WHO/MDT was discontinued. Upon hospital admission were observed fever (38.6 ºC, axillary's temperature), weight = 34 kg, jaundice, oral erosions, conjunctivitis, generalized lymphadenopathy, hepatoesplenomegaly, morbiliform rash and edema of face, ankles and hands. The main laboratory data on admission included: hemoglobin, 8.4 g/dL; WBC, 15,710 cells/mm^3, without atypical lymphocytosis or eosinophilia; platelet count, 100,000 cells/mm^3; serum aspartate aminotransferase, 1,013 IU/L [reference value (RV) ≤ 46 IU/L]; alanine aminotransferase 1,406 IU/L (RV ≤ 38 IU/L); gamma-glutamyl transpeptidase, 228 mg/dL (RV ≤ 35 mg/dL); alkaline phosphatase, 672 IU/L (RV ≤ 447 IU/L); direct bilirubin, 21.5 mg/dL (RV ≤ 0.2 mg/dL); indirect bilirubin, 5.6 mg/dL (RV ≤ 0.8 mg/dL) and INR = 1.49 (RV ≤ 1.25). Following, the clinical conditions had deteriorated, developing exfoliative dermatitis, hypotension, generalized edema, acute renal [creatinine = 1.76 mg/dL (RV ≤ 1.1 mg/dL); urea = 62 mg/dL (RV ≤ 47 mg/dL)] and hepatic failure (INR = 4.87), pancytopenia, intestinal bleeding, needing adrenergic drugs, replacement of fluids and blood product components

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(red blood cells, platelets and frozen fresh plasma) and antibiotics due to pneumonia, urinary tract infection (*Escherichia coli* and *Serratia marcescens*), and bacteremia (*Enterococcus faecium*). Ten days after admission she started to improve. Subsequent laboratory studies revealed normal or negative results: Hepatitis A, B, C; CMV and EBV serological screens; CD4/CD8 ratio; serum complement (C4) level; haptoglobine; rheumatoid factor and antinuclear antibody titers. Serum tests for blood dapsone level, methemoglobin, glucose-6-phosphate dehydrogenase assay, skin biopsy, treatment with corticosteroids or dapsone provocation tests were not performed. At day 31st of hospitalization, she restarted treatment with clofazimine and rifampicin without any adverse effect, and was discharged to home at day 39th. Before start these drugs, high IgE levels (> 500 IU/mL; RV < 100 IU/mL) and eosinophilia (3,364 cells/mm^3; RV < 500 cells/mm^3) were observed. The patient remains under supervised treatment for leprosy, with good outcome.

DISCUSSION

Drugs most frequently causing hypersensitivity syndrome include anticonvulsants, such as phenyntoin and carbamazepine; sulphonamide antibiotics and sulfones[18]. DHS is characterized by the sudden onset of papular or exfoliative rash, accompanied by fever, malaise and weakness, followed by jaundice, tenderness of liver and lymphadenopathy, resembling infectious mononucleosis. Anemia, oral erosions, conjunctivitis, splenomegaly, eosinophilia, atypical lymphocytosis, and rise of liver enzymes are other corroborative findings[1-5,7-8,14,17-25]. It is important emphasize that all those features need not necessarily be present[10,12,14,18-19,21,25]. LETA *et al.*[14], performed a systematic review of the diagnostic criteria for DHS (33 papers, N = 105 cases, 1956-2001), showing that 59% of these 105 cases could be classified as complete DHS forms (fever, rash, lymphadenopathy and hepatitis). This study also revealed that most of the patients with complete DHS forms presented leprosy (90%), classified as paucibacillary (71%)[14]. In general, DHS occur three to six weeks after start the administration of dapsone, and subside with the cessation of this drug[12,14,18]. The course of DHS is variable, but it may last for four weeks or more[12,14,18], being fatal in some cases[7-9,14,20,23], with a mortality rate estimated in 13%[14]. In addition, intercurrent infections may worse the clinical outcome[8], similar to herein described.

There has been observed an increase in the reports of DHS in the past few years, and it has been associated with the introduction of WHO/MDT for leprosy world-wide[11,14,19-20]. This apparent increase in DHS case reports depends on multiple factors and are probably related to the significant decrease of the prevalence of leprosy world-wide after introduction of MDT - from around 5,4 million to less than 0.53 million at the beginning of 2003[26], determining an increase of voluntary reporting of leprosy patients, associated to improvements in organization of leprosy controls and awareness among physicians of DHS[19].

The real incidence of DHS is not known. According to the review performed by RAO & LAKSHMI, it probably ranges between 1-4% of the patients using WHO/MDT[19]. Brazil is the second most endemic country of leprosy in the world with a prevalence rate of 4.2/10,000 population[26]. Among newly detected cases reported of leprosy world-wide, about 13% are children bellow the age of 15[26]. Bibliographic review showed 17 cases of DHS reported by Brazilian authors (Table 1), all of them in patients with leprosy, with two deaths[2,3,6,9,13,17,23]. Patient's age was only cited in the four case reports, being one in a 12 y old child. Although speculative, these data could suggest that DHS is being sub-notified or not diagnosed.

The pathogenesis of the DHS remains unknown. There is some evidence to suggest that metabolic differences in the production (eg., increased activity or quantity of polymorphic enzymes of cytochrome P450) and detoxification of reactive metabolites (e.g., glutathione synthetase deficiency), play an important role in sulphonamide hypersensitivity reactions[18]. Production of a toxic metabolite (hydroxylamine) due to an unbalance between alternative routes of dapsone metabolism [aceylation (decreased) and hydroxylatylation (rapid)], have been considered as risk factors for hemolytic anemia[4]. The influence of a particular disease state on a susceptibility to a hypersensitivity reaction is another potential factor, such as the cellular immunodeficiency observed in patients with lepromatous leprosy, and history of allergy[8,21]. Positive lymphocyte stimulation test and predominantly activated cytotoxic T cells in the dermis of a DHS patient with skin involvement have also suggested an allergic rather than idiosyncratic reaction[22]. The patient's past medical history revealed allergy to some cooling drinks. In addition, eosinophilia and high IgE levels were observed during outcome.

Table 1
Cases of dapsone hypersensitivity syndrome reported by Brazilian authors

Reference (period)	Model of study	Age (y)	Periodical indexed	DHS (N)	Disease	Deaths
Opromolla & Fleury, 1994[17]	CR	67	LILACS	1	Leprosy	1
Gallo, Nery & Garcia, 1995[9](1986-1994)	Adverse effects of WHO/MDT	NR	LILACS	3/980	Leprosy	0
Brasil *et al.*, 1996[6](1991-1993)	Adverse effects of WHO/MDT	NR	Medline	0/20,667	Leprosy	*
Andrade *et al.*, 1999[2]	CR	12	LILACS	1	Leprosy	0
Barbosa *et al.*, 2000[3]	CR	49	LILACS	1	Leprosy	0
Santos *et al.*, 2002[23](1990-2001)	CS	NR	Abstract	10	Leprosy	1
Lastória *et al.*, 2004[13]	CR	53	NI	1	Leprosy	0
Total			7	17		2

DHS, dapsone hypersensitivity syndrome; MDT, multidrug therapy; CR, case report; CS, case series; NR, not reported; NI, not indexed; *, two deaths related to rifampicin.

Prompt withdrawal of dapsone, supportive measures and minimal use of other drugs are essential in the management of DHS[12]. Anecdotal experience has resulted in the widespread use of corticosteroids in DHS[2-3,10,12,18,21-25], although no controlled studies have been performed to evaluate it effectiveness. According to some authors, tapering regimens of systemic corticosteroids are advised because dapsone persists for up to 35 days in organs via protein binding and enterohepatic circulation[10,12,18,24-25]. Preliminary results have pointed that corticosteroids have not interfered in the outcome of DHS[14]. However, methodological limitations preclude conclusions about this feature, since no analysis were performed considering the correlation among type and doses of corticosteroids, associated severe infections and outcome for each case[14].

Considering the potential hazards of rechallenge test with dapsone[2,10,12], we accepted our patient's overall clinical picture consistent with complete DHS. An isolated adverse reaction to rifampicin may be excluded, which is known to be hepatotoxic and nephrotoxic[6], since the patient restarted supervised treatment for leprosy with this drug without adverse effects. However, we cannot rule out the possibility of interaction between rifampicin and dapsone inducing the liver damage[14].

In conclusion, physicians, mainly in geographical areas with high prevalence rates of leprosy, should be aware to this potentially fatal, and probably not so rare, hypersensitivity reaction to dapsone.

RESUMO

Síndrome de hipersensibilidade à dapsona em uma adolescente durante tratamento de hanseníase

Menina, 12 anos, foi admitida referindo o uso de esquema de poliquimioterapia preconizado pela OMS para tratamento de hanseníase forma multicibacilar (dapsona, rifampicina e clofazimina) há 24 dias, apresentando icterícia, linfadenomegalia generalizada, hepatoesplenomegalia, conjuntivite, úlceras orais, exantema morbiliforme e edema de face, mãos e tornozelo. Os principais achados laboratoriais à admissão incluíam: hemoglobina, 8,4 g/dl; leucograma, 15.710 céls/mm^3; contagem de plaquetas, 100.000 céls/mm^3; RNI = 1,49; aumento dos níveis séricos da alanino e aspartato aminotransferases, gama-glutamil transpeptidase, fosfatase alcalina e bilirrubinas. Em seqüência, ocorreu piora do quadro, desenvolvendo dermatite esfoliativa, choque, edema generalizado, insuficiências renal e hepática, pancitopenia, sangramento intestinal, pneumonia, infecção urinária e bacteremia, necessitando de drogas adrenérgicas, antibióticos, infusão de líquidos e hemoderivados. Iniciou melhora no 10º dia de internação, recebendo alta hospitalar no 39º dia, tendo iniciado novo tratamento supervisionado para hanseníase com rifampicina e clofazimina, sem efeitos adversos. O caso relatado preenche os critérios para o diagnóstico de síndrome de hipersensibilidade à dapsona (febre, dermatite esfoliativa, linfadenopatia, anemia e acometimento hepático com necrose hepatocítica e colestase). Os médicos, principalmente em regiões com alta prevalência de hanseníase, devem estar atentos para esta grave, e provavelmente não tão rara, reação de hipersensibilidade à dapsona.

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