Symptomatic Hyperlactatemia And Lactic Acidosis As Complications Of Anti-Retroviral Therapy. An Experience From Limpopo Province, South Africa.

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Citation

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Abstract

Objective:
To determine the incidence, presentation, risk factors and mortality associated with symptomatic hyperlactatemia (SHL) and lactic acidosis (LA).Design:
Prospective, case-control.Setting:
Polokwane Provincial Hospital HIV-Clinic, Limpopo, South Africa.Subjects:
All adult patients on anti-retroviral therapy, from January to December 2006.Results:
Seventeen cases were found to be compatible with SHL or LA, 14 and three respectively, for a combined incidence of 20.2 per 1000 patients per annum. Most cases were female of 43 years on average. Digestive symptoms were the presenting complaint in 90 % of cases. A sensory-distal-symmetrical peripheral neuropathy was found in 65 % of cases; 50 % showed signs of lipodystrophy. All cases of SHL survived but two with LA died. We found female, older than 30, obese, presence of polyneuropathy and/or lipodystrophy and a CD-4 count of more than 200/mm^3 as risk factors that identify those patients more likely to develop SHL or LA.
Conclusion: Anti-retroviral therapy-associated
LA
has a high mortality. The presence of digestive symptoms in a patient with risk factors such as: female, obese, already on treatment for several months, should alert the physician about the possibility of SHL or LA.

Note: A version of this study was presented in a scientific forum that took place in the Walter Sisulu University, Mthatha, in 2008 but it has never been published totally or partially.

INTRODUCTION

The development of anti-retroviral therapy (ART) has been considered one of the most significant achievements of Medicine in the last decades; but these drugs are also very toxic and potentially deadly. In the case of nucleoside reverse transcriptase inhibitors side-effects are usually due to mitochondrial toxicity. SHL and LA are just two among the various possible complications.[1]

Observational studies have reported some risk factors associated with SHL/LA: female gender, obesity, other signs of mitochondrial toxicity (lipodystrophy, polyneuropathy, fatty liver, myopathy, and pancreatitis), normal CD-4 count and treatment for months or years.[2]

Limpopo province has a population of six millions, the estimated prevalence of HIV is eight per cent (8%), and therefore about half a million infected people are expected. If we consider that the prevalence of symptomatic hyperlactatemia and lactic acidosis has been estimated to be 0.4 to 9 % and 0.1 to 0.4%, respectively, at least a few hundred cases can be anticipated every year. [3•][1•]

To the best of our knowledge only two studies from South African patients covering this topic have been published, but none from our province.[1•]

Which is the incidence of SHL and LA among patients on ART in Limpopo Province?

How do they present? Which are the risk factors associated to these conditions? Which has been their prognosis once diagnosed and treated? The aim of our study was to try to answer these questions.

METHODS

We conducted a prospective, case-control, study of all cases on ART which developed a clinical and humoral picture compatible with LA and SHL , seen at the HIV Clinic, Department of Family Medicine, Limpopo province South Africa, from January to December 2006. Data from all patients are kept in an electronic database.

Inclusion criteria: all patients on ART, any combination, seen at the above mentioned institution from January to December, both months included, who developed SHL or LA. Both conditions were defined according to the Southern African HIV Clinician Society recommendations.

Exclusion criteria: all cases in which an alternative explanation other than ART for LA or SHL were found.

Control group: all patients on ART who did not develop hyperlactatemia or LA attributed to ART or any other condition.

All patients were treated according with the Southern African HIV Clinician Society recommendations.

Statistical analysis: Data analysis was performed with Epi-info software from the CDC, Atlanta, version 3.3.2, 2005. The X^2 test, or Fisher's exact test when necessary, was used to assed the association between categorical variables. Statistical significance was considered if $p<0.05$.

RESULTS

During a 12 months period 860 patients were on ART, from 35 of them lactic acid measurement were obtained due to a clinical picture suggestive of SHL or LA; on further re-assessment 18 cases were excluded because and alternative explanation was found other than ART toxicity. Table 1

Figure 1

Table1. Causes of high lactic ac. other than ART

Condition	N	%
Acute diarrhea	9	50.00
Renal failure	3	16.6
Cryptococcus meningitis	2	11.1
Disseminated tuberculosis	2	11.1
Septic bedsores	1	5.6
Cardiac failure	1	5.6
Total	18	100.0

Seventeen patients were left for analysis; the remaining 825 were taken as a control group. All 17 patients were on regimen 1A: stavudine, lamivudine and efavirenz; on the control group 61(7.4%) were on regimen 2: azidovudine, didanosine, lopinavir/ritonavir; the rest also on regimen 1A. The role of stavudine in the development of SHL/LA could not be assessed since almost all patients in both groups were on this drug.

Fourteen patients fulfilled SHL criteria and three of LA to make and incidence of 16.6 and 3.6 per 1000 per annum respectively; 20.2 combined.

The mean age was 43 years, whereas on the control group it was 32, table 2. We found the association of the category older than 30 years, with the presence of SHL and LA, to be significant, $p<0.005$.

Regarding sex distribution 16 cases were females, 95 %. ($p<0.05$) Table 2

The mean time elapsed since ART started until diagnosis was eight months, but as early as five and as late as 20; in most cases, 80%, it was between five and twelve months, table 3.

Distribution of presenting symptoms can be seen in table 4. Most patients presented with gastrointestinal symptoms, but loss of weight was also very common. Dyspnea was always found in all cases of LA and one of SHL.

The physical findings have been grouped as specific syndromes and signs, table 2. Polyneuropathy, always sensory-distal-symmetrical, and lipodystrophy were found in more than 50 % of cases.

At the time of diagnosis of these complications the CD-4 count was found significantly higher in the study group, Table 5

Arterial blood gases parameters and lactic acid values can be seen in Table 2.

The response to treatment was excellent in SHL, 100 %, but very disappointed in LA, two died, only one survived.

Figure 2

Table 2. Characteristics of patients

Parameter	Study group	Control group	p value
Demographics			
Mean age (Range)	42.88 (33-60)	32.26 (15-85)	
Patients ≥30 years of age (%)	14 (82.4)	399 (48.2)	<0.005
Female gender N (%)	16 (94.1)	570 (69.0)	<0.05
Male gender N (%)	1 (05.9)	255 (31.0)	
Physical signs and associated conditions			
Body weight, Kg. mean (range)	73.50 (53-102)	54.40 (35-82)	
BMI mean (range)	28.22 (19-37)	19.10 (15-41)	
BMI >30 N (%)	6 (35.3)	82 (9.9)	<0.0008
Polyneuropathy N (%)	11 (64.7)	42 (5.1)	<0.0000005
Lipodystrophy N (%)	9 (52.9)	21 (2.5)	<0.0000005
Abdominal distention N (%)	4 (23.5)	NA	
Hepatomegaly N (%)	2 (11.8)	NA	
Laboratory (mean)			
ALT	37 UI/L	32 UI/L	
Total protein	72 g/L	69 g/L	
Albumin	41 g/L (>35)*	32 g/L	<0.05
Glucose	5.2 mmol/L	NA	
Creatinine	86 µmol/L	79 µmol/L	
Cholesterol	3.8 mmol/L	3.5 mmol/L	
Triglycerides	0.9 mmol/L	0.7 mmol/L	
CD-4 count first visit at time of Dx	 107 255 (>200)*	 82 162	 <0.005
*Value arbitrarily chosen for comparison			
BMI: body mass index NA: not available			

Figure 3

Table 3. Time from ART starts until diagnosis

Time (months)	N	%
5-8	9	52.9
9-12	5	29.4
13-16	2	11.6
17-20	1	5.9
Total	17	100.0

Figure 4

Table 4. Distribution of symptoms

Symptoms	N	%
Abdominal pain	15	88.2
Nausea	13	76.4
Poor appetite	12	70.5
Loss of weight	12	70.5
Vomiting	10	58.8
Shortness of breath	4	23.5

Figure 5

Table 5. Arterial blood gases and lactic acid values

Parameter	SHL N:14		LA N:3	
	mean	(range)	Mean	(range)
Lactic acid (mmol/L)	4.6	(2.9-8.3)	12.3	(8.2-16.4)
Bicarbonate (mmol/L)	24.6	(20.1-29.6)	7.1	(5.2-10.4)
Anion gap (mmol/L)	11.3	(7-13)	22.2	(18-34)
pH	7.38	(7.35-7.48)	7.08	(6.9-7.16)

DISCUSSION

Calza et al, in a review article, report an incidence of four to 90 per 1000 per annum regarding SHL and from one to four for LA, wide ranges indeed, which with our own findings coincide. In another study conducted in London, and therefore a very different population from ours, but with a sample of similar size, Moyle et al found an incidence of 13.6 for SHL, similar to our finding, but 12.2 for LA, almost four times ours; they explain this high incidence by the use of didanosine, certainly this NRTI has been considered the most toxic of all. Although it is part of the regimen 2 used in South Africa, very few patients were on it, 61 out of 860. Two studies conducted on South African patients have been published; one from Soweto reported an incidence of 20.2 and 10.6 regarding SHL and LA respectively; the second from Kuazulu-Natal 19 per 1000 per annum of LA only, they didn't report of SHL. Both studies reported higher incidence of LA than our findings, might be in relation to a more exhaustive search for it as a consequence of their experience since they started using ART few years before the rest of country. To the best of our knowledge the only study conducted in Africa, outside South Africa, is from Uganda; from the reported data we calculated an incidence of 2.14 and 4.3 per thousand per annum regarding SHL and LA respectively.[1] Call our attention the low incidence of SHL, it can be explained by the criteria they used since only those patients with two or more symptoms underwent lactic acid measurement, today we know that many patients are monosymptomatic at the time of presentation. [11]

Our series shows a mean age a bit higher than most published studies, we think that the reason is that there was a single cases of 60 years, being our group small one case can create a great impact statistically, if that case is not considered the mean age comes down to 39, which is very close to previous reports. In six studies published, two of them from South Africa the reported mean age was between 36 and 38 years; in the case of European and American reports we could think that they just reflect the age of the

groups where prevalence is highest but even in Africa, where the maximum prevalence of HIV-AIDS is found at a considerably younger age, between 25-29, the incidence of SHL and LA is found at the same age reported in non-African studies.[11,12] This fact makes us think that other factors not necessary related to the viral infection itself could play a role on these metabolic events.

Regarding sex our results are similar to other reports from Africa in which females accounted for 80 to 100 % of cases.[1] Contrary to our results, some reports from Europe, America and Australia found a frank predominance of males. [11,13,1] At first sight a simple explanation could be found in the demographic distribution of HIV in different geographic regions but the same result has also been found in one study from outside the African continent, where, despite not being the female the predominant gender in the HIV population, it was found the most affected by these disorders.[1] The predominance of female regarding this metabolic complications goes beyond the simple demographic representation because almost all studies, report a frank predominance of women. It has been postulated that there are pharmacodynamics differences between genders, being the renal clearance of many drugs, including antiretroviral, slower in females which would increase the time of exposure of susceptible tissues to potentially toxic drugs Hormonal differences could also play a role. We think that more research is needed to clarify this issue.

Overweight and obesity have been proposed as risk factors for the development of SHL/LA; in Kwazulu-Natal and Soweto studies the mean weight was 85 Kg, in the former, and obesity of 30 %, in the latter, we found comparable figures.[1] The reason why overweight and obese people are more prone to develop these complications is not known, in fact most of them experienced loss of weight before other symptoms commence. We postulate that being the main source of fatty acids increased, the adipose tissue, there is greater amount of these acids that cannot be catabolized by the mitochondria increasing lactic acid formation and perpetuating the acidotic state; in other words we think the increased adipose tissue facilitate lactic acid formation but it is not the primary cause of the metabolic dysfunction itself.

The symptoms in SHL/LA depend on mitochondria inactivity or destruction, it's well known that they have a very variable life span, from days to months, they can also regenerate, and that's why symptoms and signs of toxicity show up after a prolonged exposure to toxic drugs. In South Africa three studies report cases as early as two months and as late as two years, with an average from seven to ten months, our data coincide with those studies. [1] We should highlight that a great deal of clinical suspicion is necessary to relate certain symptoms with drugs that have been used for month, even years, being apparently well tolerated; this prolonged latency period make the diagnosis very difficult.

Almost all of our patients presented with gastrointestinal symptoms, table 4, all reviewed studies present the same findings. [1,11] [13]

It is considered that the liver is the most affected organ, which undergo fatty degeneration, both macro and microvesicular; its central metabolic role, together with the metabolic acidosis, would explain the digestive symptomatology. [2,1] [1] The loss of weight, we think, could be caused by the sustained acidosis, vomiting and loss of appetite; furthermore, the anorexia diminishes carbohydrate intake which increases lipid catabolism worsening the acidotic state. Dyspnea was associated to cases of LA; always expected in metabolic acidosis, but it was also found in one case of SHL, the latter with the highest level of lactic acid in this group.

Polyneuropathy and lipodystrophy were found in more than 50 % of cases whereas in the control group only in five and three percent respectively. These figures coincide with what has been reported nationally and internationally. [1]

Up to 30 % of HIV patients may suffer of peripheral nervous system complications, despite being on ART or not; mainly a sensitive-symmetrical-distal polyneuropathy; this kind of polyneuropathy can be caused by multiple conditions in this type of patients, among others: infections (VIH), toxics (TB treatment, ART), metabolic diseases (uremia, diabetes), nutritional deficiencies (cobalamin, thiamine, pyridoxine), which make the differential diagnosis very difficult, even if nerve conduction tests and nerve biopsy are available.[2] Surprisingly, despite the high prevalence of peripheral neuropathy in patients with AIDS worldwide the figures reported from our control group are rather low; we found it in just 5% of cases in the control group, however in South Africa it has been associated in up to 40 % of patients. We think that there is an underdiagnosis probably due to low index of suspicion and inadequate examination. We should state that all patients with a provisional diagnosis of SHL/LA were re-examined by one of the authors (MZM), so

there could be bias in favor of the study group.

Lipodystrophy was also significant; it has been associated with hyperlipidemia and hyperinsulinemia. Mitochondrial toxicity has been considered, protease inhibitors are a better established cause but even non-treated patients can suffer it. [21]

Our results coincide with various authors that have identified a high CD-4 count as a marker for patients with SHL/LA, no clear explanation exist for this finding. [•] No all researchers found the same; on the contrary, Bonnet et al, in France, and Coghlan in Birmingham, USA, report a low CD-4 count as an indicator of bad prognosis regarding SHL/LA. [12,22] More studies with bigger sample might clarify this issue.

The data show that these entities, although clinically very similar, can be separated with the help of the lab in two conditions with different treatment and prognosis. [11,22]The differentiation is important because SHL is a less severe stage of the metabolic derangement that can be stopped for going in to LA, the latter with a far worse prognosis.

Regarding mortality our findings are not very different from those reported internationally. Moyle et al report 50 % mortality for LA and none for SHL, while the Birmingham study found also almost 50 % mortality in total but with two SHL patients and three LA out of twelve cases. [·22] Other studies had reported up to 100 % mortality for LA, which represent a late stage in which all compensatory mechanisms have failed, lactic acid descends the pH to levels so low that enzymatic mechanisms stop functioning and multiorgan failure ensues. [22]The somehow better mortality reported in recent studies can be explained by an earlier diagnosis, because in term of treatment nothing effective is available. [

CONCLUSION

The presence of digestive symptoms in a patient who has been on ART for at least a few months, especially if female, overweight or obese, who responds well to treatment, should alert the clinician about the possibility of SHL/LA. Because mortality is so high in LA early diagnosis while still on the phase of SHL is mandatory.

The current substitution of stavudine by tenofovir might reduce the incidence of these serious ART complications.

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