International Journal of Infectious Diseases 45 (2016) 46–52

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Exploratory urinary metabolomics of type 1 leprosy reactions

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ARTICLE INFO

Article history:
Received 1 January 2016
Received in revised form 12 February 2016
Accepted 16 February 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Biomarkers
Diagnostics
Leprosy
Metabolomics
Reactions
Urine

SUMMARY

Background: Leprosy is an infectious disease caused by *Mycobacterium leprae* that affects the skin and nerves. Although curable with multidrug therapy, leprosy is complicated by acute inflammatory episodes called reactions, which are the major causes of irreversible neuropathy in leprosy that occur before, during, and even after treatment. Early diagnosis and prompt treatment of reactions reduces the risk of permanent disability.

Methods: This exploratory study investigated whether urinary metabolic profiles could be identified that correlate with early signs of reversal reactions (RR). A prospective cohort of leprosy patients with and without reactions and endemic controls was recruited in Nepal. Urine-derived metabolic profiles were measured longitudinally. Thus, a conventional area of biomarker identification for leprosy was extended to non-invasive urine testing.

Results: It was found that the urinary metabolome could be used to discriminate endemic controls from untreated patients with mycobacterial disease. Moreover, metabolic signatures in the urine of patients developing RR were clearly different before RR onset compared to those at RR diagnosis.

Conclusions: This study indicates that urinary metabolic profiles are promising host biomarkers for the detection of intra-individual changes during acute inflammation in leprosy and could contribute to early treatment and prevention of tissue damage.

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1. Introduction

Leprosy is a complex infectious disease often resulting in severe, life-long disabilities.[1] It presents in different clinicopathological forms[2,3] and is considered a major threat in developing countries by the World Health Organization (WHO), remaining endemic in Africa, South America, and Asia. Every year approximately 220 000 new patients are still diagnosed, and this incidence rate has been essentially stable over the last decade. Furthermore, with increasing migration, new cases are also being detected in developed countries, where initial misdiagnosis is likely to occur.[4–6]

Although leprosy can be treated effectively with multidrug therapy (MDT), it is complicated by acute inflammatory episodes called leprosy reactions. These immunological complications, occurring before, during, and after treatment in 30–50% of the patients, represent the major cause of leprosy-related neurological damage.[7,8] Two types of reaction are recognized: reversal reactions (RR) or type 1 reactions and erythema nodosum leprosum (ENL) or type 2 reactions. RRs, which affect 30% of leprosy patients at least once,[9] coincide with characteristic CD4+ T-cell infiltrations of skin and nerve lesions.[10,11] Prompt diagnosis and treatment aids recovery significantly, thereby reducing the risk of permanent disability.[12,13] Unfortunately, reactions are frequently misdiagnosed due to decreased expertise within integrated health services.[9] Therefore, sensitive tests based on dependable biomarkers for early diagnosis of reactions are urgently needed.

Since leprosy endemic areas are often lacking in sophisticated laboratories, it is imperative to develop diagnostic tests that are suitable for the field setting. Similarly, home-monitoring of chronic diseases with inflammatory episodes requires ease in test performance. Besides the selection of suitable biomarkers, an

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http://dx.doi.org/10.1016/j.ijid.2016.02.012
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important prerequisite for such tests is the ease of obtaining samples. Using urine samples rather than venous blood will avoid the need for a trained phlebotomist, reduce costs, and improve ease of use. However, host-derived biomarkers for mycobacterial diseases based on urine have not yet been reported.

The rapidly evolving field of metabolomics provides a technological basis for the comprehensive analysis of urinary metabolites and the discovery of disease-associated biomarkers in urine. The feasibility of the approach has already been established in clinical studies.[14,15] Indeed, it has been shown that the metabolic composition of urine reflects the physiological status of an organism and as such can be a useful readout of multiple (patho)physiological processes.[14–16]

To investigate whether disease-specific metabolites could be detected in urine, as a non-invasive body fluid, and to identify associations between such urinary metabolites and the occurrence of leprosy reactions, an exploratory metabolomics analysis was performed in leprosy patients in Nepal.

2. Materials and methods

2.1. Study participants

Recruitment took place in Nepal (Mycobacterial Research Laboratories, Kathmandu).[17] Leprosy prevalence was 1.1–0.79/10 000, new case detection rate (NCDR) 1.67– 1.15/10 000 (Annual Report 2012–2013, Leprosy Control Division, Department of Health Services, Kathmandu). Patients and healthy individuals from the same area (endemic controls) were recruited on a voluntary basis between February 2008 and March 2013 (Tables 1 and 2). Leprosy was diagnosed based on clinical, bacteriological, and histological observations and classified by skin biopsy according to Ridley and Jopling.[1] Clinical monitoring for reactions was performed during monthly clinic visits. Clinical and demographic data were collected in databases with a special emphasis on standardizing data collection and the definition of reactions between the cohorts. For patients who presented with a reaction, the type, severity, skin and/or nerve involvement, number of lesions, and relapse were noted in accordance with state-of-the-art clinical expertise and international consensus scoring.[18] Endemic controls were assessed for the absence of clinical signs and symptoms of leprosy and tuberculosis (TB). Staff of leprosy and TB clinics were excluded.

2.2. Ethics

This study was performed in accordance with the Declaration of Helsinki (2008 revision). Participants were informed about the

Table 1
Study cohort in Nepal[a]

Category[b]	Number	Leprosy type	
EC	34	-	
No Rxn t = 0	28	16 TT/BT	12 BL/LL
No Rxn t = end	11	4 TT/BT	7 BL/LL
RR t = 0	7	3 BT	4 BL/LL
RR t = x	24	12 BT	12 BL/LL
RR t = end	19	8 BT	11 BL/LL
Total	123		

TT, tuberculoid; BT, borderline tuberculoid; BL, borderline lepromatous; LL, lepromatous.

[a] Newly diagnosed leprosy patients without reactions (no Rxn) were sampled before (t = 0) and after treatment (t = end); leprosy patients developing reactions during the study were sampled in the absence of any clinical signs of reactions and at least 3 months before RR (t = 0), at RR diagnosis before steroids (t = x), or after multidrug therapy and RR at least 1 month after the end of steroids (t = end).

[b] EC, endemic control; Rxn, reaction; RR, reversal reaction.

Table 2
Endemic control (EC) and patient information

	PGL-I (OD)
EC	0.025
EC	0.073
EC	0.008
EC	0.020
EC	0.059
EC	0.041
EC	**0.153**
EC	0.004
EC	0.017
EC	0.006
EC	0.003
EC	0.093
EC	0.035
EC	0.019
EC	0.036
EC	0.032
EC	0.014
EC	**0.258**
EC	**0.179**
EC	**0.233**
EC	0.000
EC	0.008
EC	0.006
EC	0.000
EC	**0.568**
EC	**0.257**
EC	0.024
EC	0.046
EC	0.000
EC	0.012
EC	0.066
EC	0.019
EC	**0.203**
EC	0.147

		PGL-I (OD)	classification
no Rxn	t = 0	0.050	TT/BT
no Rxn	t = 0	0.045	TT/BT
no Rxn	t = 0	**2.919**	BL/LL
no Rxn	t = end	**1.325**	BL/LL
no Rxn	t = 0	0.078	TT/BT
no Rxn	t = 0	**0.636**	TT/BT
no Rxn	t = 0	**3.146**	BL/LL
no Rxn	t = 0	0.009	TT/BT
no Rxn	t = 0	**0.203**	TT/BT
no Rxn	t = end	0.057	TT/BT
no Rxn	t = 0	0.020	TT/BT
no Rxn	t = 0	**3.147**	BL/LL
no Rxn	t = 0	**1.349**	BL/LL
no Rxn	t = 0	**1.700**	BL/LL
no Rxn	t = 0	0.055	TT/BT
no Rxn	t = 0	0.032	TT/BT
no Rxn	t = 0	**0.225**	TT/BT
no Rxn	t = 0	**2.550**	BL/LL
no Rxn	t = end	**1.309**	BL/LL
no Rxn	t = 0	**0.305**	TT/BT
no Rxn	t = end	**0.190**	TT/BT
no Rxn	t = 0	**0.199**	TT/BT
no Rxn	t = end	0.118	TT/BT
no Rxn	t = 0	0.010	TT/BT
no Rxn	t = 0	**2.565**	BL/LL
no Rxn	t = end	**0.304**	BL/LL
no Rxn	t = 0	**0.193**	BL/LL
no Rxn	t = 0	**3.012**	BL/LL
no Rxn	t = end	**2.025**	BL/LL
no Rxn	t = 0	**1.229**	BL/LL
no Rxn	t = end	0.020	BL/LL
no Rxn	t = 0	0.117	TT/BT
no Rxn	t = end	0.034	TT/BT
no Rxn	t = 0	**0.803**	BL/LL
no Rxn	t = end	**0.315**	BL/LL
no Rxn	t = 0	**1.161**	BL/LL
no Rxn	t = end	**nt**	BL/LL
no Rxn	t = 0	**0.159**	TT/BT
no Rxn	t = 0	**0.171**	TT/BT

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