Hansen’s disease in a general hospital: uncommon presentations and delay in diagnosis

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Abstract
Background The question was raised as to why ‘obvious’ signs of leprosy, Hansen’s disease (HD), are often missed by medical doctors working in a HD endemic area.
Methods This study describes a small sample of patients who were diagnosed with HD during their hospital admission and not before. The discussion is whether the typical early signs and symptoms of HD are just not recognized, or whether unusual presentations confuse the attending physician.
Results A total of 23 HD patients were hospitalized during the study period, of which 6 (26%) were only diagnosed with HD during their admission. All were classified as lepromatous leprosy (LL) with a history of signs and symptoms of HD. In nearly all patients, a suspicion of HD might have been raised earlier if a careful history and dermato-neurological examination had been done.
Conclusions Multibacillary (MB) HD, especially close to the lepromatous end of the spectrum, may mimic other diseases, and the patient can not be diagnosed without a biopsy or a slit skin smear examination. Clinicians working in a HD endemic area (Rio de Janeiro) do not always include HD in their differential diagnosis, especially when the clinical presentation is unusual. HD should be considered in all patients with skin lesions not responding to treatment, especially when they have neurological deficits, and live or have lived in an HD endemic area. Due to the increase in global travel and immigration, doctors in low endemic areas need to consider HD as a possible diagnosis.

Keywords
delay in diagnosis, Hansen’s disease, leprosy, uncommon presentation

Conflicts of interest
None declared

Introduction
Early diagnosis of leprosy, Hansen’s disease (HD), and multidrug therapy (MDT) have a significant influence on the course of the disease, preventing and/or minimizing permanent damage and deformities.1,2 Nerve damage leading to impairments and permanent disability is still the major complication in the course of a HD infection.3 In endemic countries, the World Health Organization (WHO) has advocated the decentralization of HD control into the primary health services to improve accessibility with the expectation that this would permit early diagnosis and adequate treatment of the disease.4 However, not all primary health care services have implemented HD control activities or have the knowledge and skills to suspect early cases of the disease. Some patients continue to report late. Sometimes, an ‘obvious’ diagnosis of HD is missed even by dermatologists, especially the lepromatous form, in which the presentation is quite variable. In non-endemic countries, diagnosis often is delayed due to lack of awareness.5-9

The claimed success of the decentralization policy and elimination campaigns may lead to the false conclusion that HD is a disease of the past. It is clear that even in low- and non-endemic areas (Europe, North America), new patients with HD will continue to appear due to the increase in global travel and migration.
Rio de Janeiro is one of the 27 states of the Federal Republic of Brazil and has a population of 15 million. Almost three quarter of the population lives in Rio city and its greater metropolitan area. In 2005, Rio de Janeiro diagnosed 2947 new HD patients with a detection rate of 1.9 per 10 000. Santa Casa de Misericórdio General Hospital is centrally located in the old quarters of Rio city and is a referral and teaching hospital offering a wide range of specialist services; it also provides opportunities for internships, residencies and postgraduate training. It is one of the main referral centres for HD in the city and metropolitan area of Rio de Janeiro. It provides free hospitalization and outpatient services to persons affected by HD. Annually, approximately 60–70 new HD patients are diagnosed, and another 120 patients are treated for complications in the outpatient department (OPD). An earlier study by a group from Santa Casa showed that of 66 HD patients hospitalized 15 (23%) were diagnosed with HD only after admission to the hospital. The HD patients, who were admitted to the hospital for other reasons and only diagnosed during their hospitalization, are presented in this paper in more detail. The question is raised why so often ‘obvious’ signs of HD are missed by clinicians in an endemic area.

Materials and methods
This prospective study was carried out by two medical students, who registered all HD patients hospitalized in Santa Casa over a 20-month period during the years 2004–2005. The study included both patients already diagnosed with HD before admission and those only diagnosed with HD after admission to the hospital. Patients in this study were mainly referred from clinics and hospitals of Rio city and the metropolitan area or from one of the OPD clinics of Santa Casa. If the patient was known to have HD but was not admitted to the dermatology department, the attending physician requested a dermatology consult. A referral to a dermatologist for assessment of a skin condition also occurred when the patient was not known to have HD and had not been admitted through the dermatology department. When the main problem was HD, the patient was transferred to the dermatology department for further management. A medical history, a general physical examination, including a dermatological and neurological assessment, a slit skin smear and biopsies were taken to diagnose and classify the HD patients. Further laboratory investigations were done when indicated. Photographs of special skin conditions were taken for teaching purposes. Routine procedures were followed; no laboratory or other interventions specific for this study were carried out.

Definitions
The HD classification takes notice of a variety of clinical forms. The most common classification system used by specialist HD services is the Ridley-Jopling (RJ) system which originally was developed based on the at the time understanding of the immunopathology. The RJ spectrum ranges from indeterminate (I), tuberculoid (TT), via tuberculoid-borderline (BT), borderline-borderline (BB), borderline-lepromatous (BL), to lepromatous (LL). With the introduction of multidrug therapy (MDT) by the WHO in 1982, a new classification system for control programmes was introduced and the disease classified as paucibacillary (PB) or multibacillary (MB) HD. PB are patients with less than six skin lesions and a negative skin smear, MB are patients having six or more skin lesions and/or a positive skin smear. MDT for PB contains Rifampicine 600 mg once monthly and Dapsone 100 mg daily for 6 months; MDT for MB contains Rifampicine 600 mg and Clofazimine 300 mg once monthly with Dapsone 100 mg and Clofazimine 50 mg daily for 12 months.

Uncommon presentation refers to less frequent signs and symptoms which differ from the main clinical signs but nevertheless are typical of HD (e.g., diffuse lepromatous HD – Lucio’s Leprosy and rheumatic manifestations).

Atypical presentation refers to an unusual presentation and therefore surprise finding of HD (e.g., suspected lymphoma).

Systemic involvement refers to the fact that HD is not limited to skin and peripheral nerves, but involves other structures, including the mucous membranes of the upper respiratory tract, the eyes, intra-abdominal organs, lymph nodes, bone marrow, testicles, muscles, joints, bones, etc.

Data collection and analysis
Patient data were collected on special designed forms (history, general physical examination, dermatological and simplified neurological evaluation) together with the routine forms for laboratory investigations (e.g., haematology, liver and renal functions), skin smears and biopsy. Due to a limited number of patients, there was no need for a data-based statistical computer program.

Ethical committee
At the time of this study, Santa Casa did not have an ethical committee, but institutional approval was obtained from the Instituto Dermatologia Prof. Rubem David Azulay and Santa Casa de Misericórdio.

Results
A total of 23 HD patients were hospitalized in Santa Casa during the period of May 2004 to December 2005. The age range was from 19 to 72 years old, with a median of 42 years and mean age of 44 years. Most patients were males (77%), and most had a MB classification (89%). Of the MB patients, 76% were classified as lepromatous leprosy (LL). Seventeen of the patients had been diagnosed prior to hospitalization, of which eight patients were still on MDT treatment (4 of those were admitted for a drug reaction to dapsone, 1 for a severe reversal reaction, 2 for a severe erythema nodosum leprosum – ENL reaction and 1 for other non-HD reasons) and nine patients were already released from anti-HD treatment (4 of those admitted for a severe ENL and 5 for
other non-HD reasons). Six patients were diagnosed with HD only during their hospital stay. No other HD patients were admitted to the hospital during the study period.

The six HD patients diagnosed during their hospital stay (Table 1):

- **Patient A** was admitted to the general ward with complaints of fever, asthenia and severe weight loss of 3 weeks duration. He also complained of paraesthesia in both hands and a rhinitis for 6 months. The result of the physical examination and laboratory tests revealed the following: infiltration of the face, extensive skin lesions (macules and erythematous nodules, which were painful on palpation) and positive skin smears (BI: 1.0). The diagnosis: HD classified as a LL form and severe ENL.

- **Patient B** was admitted to the general ward with complaints of dyspnoea and severe acral oedema. He had been on and off treatment for cardiac problems for the past 15 years. Six months prior to his hospitalization, his condition began to deteriorate with complaints of oedema and ‘cold’ hands. The admission diagnoses were as follows: congestive heart failure (CHF), Reynaud’s phenomenon and scleroderma. Except for the heart complaints, he had a history of numbness of the lower arms and hands for 10 years, numbness of the lower legs and feet for 1 year, and a planar ulcer on the left foot for 6 months. On examination, a generalized diffuse infiltration of the skin was noted, and papular lesions on the trunk and upper extremities were present. Claw hands and a left plantar ulcer were also found. The skin smear was positive (BI: 1.7). The symptoms suggesting a connective tissue disease were considered to have been due to HD. The final diagnosis was CHF and HD, classified as LL.

- **Patient C** was admitted to the dermatology ward with the diagnosis of erythroderma of 3-month duration. The patient had a history of lower leg ulcers for 5 years. On examination, in addition to the diffuse erythema, many other skin lesions and nodules, which were tender on palpation, were found on the face, trunk and extremities, compatible with ENL. The skin smear was positive (BI: 4.0). The diagnosis of HD, classified as LL, with ENL and leg ulcers as a consequence of HD was made. After the start of MDT MB and anti-reactional treatment (prednisolone and thalidomide), the erythroderma and leg ulcers improved rapidly.

- **Patient D** was admitted to the general ward with complaints of a scrotal mass and bilateral inguinal lymphadenopathy for 8 months. Besides, he complained of fever and painful nodules over the body for 3 months. A seminoma with metastases was suspected. A biopsy was taken from one of the inguinal glands, which showed no signs of a seminoma or other malignancy, and was diagnosed as lepromatous HD. On examination, diffuse infiltration of the face and widespread erythema nodosum were found. Because of the clinical signs, the skin smear (BI:2.6) and biopsy results with a.o. AFB’s and foam cells, the diagnosis of HD was made. After the start of MDT MB and anti-reactional treatment (prednisolone and thalidomide), the patient improved rapidly.

- **Patient E** was admitted to the dermatology ward presenting with fever and unusual skin lesions. These lesions included widespread papules and slightly raised, erythematous lesions, some target like, with central bullae, crustae and necrosis (Fig. 1), particularly in the face and on the extremities. No cutaneous or subcutaneous nodules were found. She developed the skin problems after taking medicines for a sore throat and stuffed nose 3 weeks earlier. As her condition deteriorated, she was admitted on suspicion of a drug eruption. The attending dermatology resident noted that in addition to the erythema multiforme-like (EM-like) lesions, there was a very fine discrete generalized skin infiltration present. No other skin lesions typical for HD were found, nor was any nerve involvement noted. The slit skin smear was positive (BI: 3.6), and the biopsy showed signs of a reaction. A diagnosis of diffuse lepromatous HD (Lucio’s Leprosy) was made, with the EM-like form of ENL. She was started on MDT MB and anti-reactional treatment (prednisolone) and improved rapidly.

- **Patient F** was admitted to the dermatology ward for chronic lower leg ulcers. The lesions existed for more than 10 years despite visits to many specialists. On examination, the patient was found without any obvious sign of HD but with a fine, reddish infiltration all over the body, scars on the

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**Table 1** HD patients diagnosed after hospital admission

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years</th>
<th>Sex</th>
<th>Duration signs and symptoms</th>
<th>Duration complaints leading to hospital admission</th>
<th>BI</th>
<th>WHO* grade</th>
<th>Final hospital diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>34</td>
<td>M</td>
<td>6 months</td>
<td>3 weeks</td>
<td>1.0</td>
<td>1</td>
<td>LL classification, severe ENL</td>
</tr>
<tr>
<td>B</td>
<td>54</td>
<td>M</td>
<td>10 years</td>
<td>6 months</td>
<td>1.7</td>
<td>2</td>
<td>LL, CHF</td>
</tr>
<tr>
<td>C</td>
<td>42</td>
<td>M</td>
<td>5 years</td>
<td>3 months</td>
<td>4.0</td>
<td>1</td>
<td>LL, leg ulcers due to HD, severe ENL</td>
</tr>
<tr>
<td>D</td>
<td>34</td>
<td>M</td>
<td>8 months</td>
<td>8 months</td>
<td>2.6</td>
<td>0</td>
<td>LL, HD, lymphadenopathy, ENL</td>
</tr>
<tr>
<td>E</td>
<td>52</td>
<td>F</td>
<td>3 weeks</td>
<td>3 weeks</td>
<td>3.6</td>
<td>0</td>
<td>Diffuse lepromatous, ENL</td>
</tr>
<tr>
<td>F</td>
<td>25</td>
<td>F</td>
<td>10 years</td>
<td>10 years</td>
<td>3.8</td>
<td>1</td>
<td>Diffuse lepromatous, leg ulcers due to HD</td>
</tr>
</tbody>
</table>

BI, Bacterial Index; *WHO disability grade.
dorsum hands and arms, slight cyanosis of the hands, and ulcerating lesions on the lower leg with oedema of the lower legs and feet (Fig. 2). A loss of fine body hair (but no madarosis) was also noticed. There was no obvious neurological involvement except for some sensory loss in the lower legs and feet. The skin smear was positive (BI: 3.8). Due to a misunderstanding, no biopsy was taken. A final diagnosis of HD, diffuse lepromatous (Lucio’s Leprosy) with chronic lower leg ulcers was made. The leg ulcers healed rapidly after the start of MDT MB, without any additional treatment.

Discussion
The question was raised why so often 'obvious' signs of HD are missed by medical doctors working in an HD endemic area, such as Rio de Janeiro. Although the numbers in this study are small, the cases are illustrative. In this group of 23 cases, 6 patients (26%) were only diagnosed during their stay in the hospital. In a previous retrospective study of Santa Casa, this percentage was 23%. All were classified as LL with a history of signs and symptoms of HD of less than 1 month to 10 years. With careful history taking and dermato-neurological examination, in most of them, the suspicion of HD might have been raised earlier. The patient (D) with inguinal glands and a scrotal mass had an atypical presentation, but also showed a diffuse infiltration and ENL nodules all over the body. All patients had been seen earlier by clinicians and some even by dermatologists (including patients E and F).

Of the 17 HD patients diagnosed before admission, still on MDT treatment or already released from treatment, 41% were hospitalized for a severe reaction (RR and ENL), 24% for adverse effects to the MDT medication and 35% for other reasons not related to HD. Even after release from MDT (RFT), HD patients are in danger of developing severe complications: 4 out of 9 such patients were hospitalized because of a severe ENL. There are no comparable studies (admission of patients with a history of HD in a general hospital) known to us except the above-mentioned previous study at Santa Casa, which also showed that the main reasons for hospitalization of known HD patients were reactions and, in a smaller percentage, adverse effects to treatment, in particular Dapsone. However, there are several studies about admissions to HD hospitals which present reactions (including neuritis) and ulcers as main reasons for admission of HD patients, with a smaller percentage for other reasons (including eye complications, surgery, fitting of orthopaedic appliances, relapses and adverse effects of chemotherapy).

Awareness of HD and early diagnosis
Many newly diagnosed patients at the Santa Casa OPD with clear signs and symptoms of HD mentioned that they had had complaints for many years, but that their complaints had been ignored when they presented themselves to the health services. Early signs and symptoms, including skin lesions and skin infiltration, numbness, sensory loss or other neurological deficits, are often not recognized, and HD is usually not included in the differential diagnosis when a patient does not respond to the initial treatment. Rogers and Muir in the third edition (1946) of their handbook 'Leprosy' already complained about this: ‘In many instances medical practitioners living in endemic areas, and holding high rank in their profession, have failed to diagnose even cases which had advanced far beyond the first stage’. Several studies suggest that HD should be considered in any patient with a non-healing skin lesion, treated for other skin diseases, particularly if they have neurological deficits or have been living in an endemic area.

A study from California, USA details the most common presentations of HD in an emergency department as: dermatological
Hansen’s disease: uncommon presentations

Table 2 Uncommon presentations

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse infiltration (Lucio’s Leprosy)</td>
<td>25, 27, 28</td>
</tr>
<tr>
<td>Diffuse oedema of fingers, hands and feet</td>
<td>25, 28, 37, 41</td>
</tr>
<tr>
<td>Palmo-plantar cyanosis</td>
<td>25, 37</td>
</tr>
<tr>
<td>Long standing leg ulcers, not reacting to common treatment</td>
<td>28, 38, 39</td>
</tr>
<tr>
<td>Longstanding rhinitis, obstruction and bloody discharge of the nose not reacting to common treatment</td>
<td>25, 35, 37, 38</td>
</tr>
<tr>
<td>Signs and symptoms of connective tissue disease (for example; systemic lupus erythematosus)</td>
<td>23, 25, 27</td>
</tr>
<tr>
<td>Rheumatic manifestations (e.g. arthritis, swollen hands syndrome, cutaneous vasculitis, myositis, with or without erythema nodosum)</td>
<td>28, 29, 30</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>31, 32</td>
</tr>
<tr>
<td>EM</td>
<td>27, 33, 34</td>
</tr>
</tbody>
</table>

(68%), neurological (23%) and ophthalmological (9%).20 These studies from the USA, Canada and Australia are all from non-endemic areas, although some have large immigrant communities originating from endemic countries.

Although in most patients the diagnosis of HD is not that difficult, it still requires skill to differentiate the HD skin lesions from other diseases and to recognize nerve involvement. A significant proportion of MB patients, specifically those close to the lepromatous end of the spectrum, cannot be diagnosed without skin smears or biopsy. Diagnosis based solely on an anaesthetic patch is likely to miss about 30% of the MB cases.20,22

Uncommon presentations

MB patients, in particular those with more general symptoms, will in general first present to clinicians and specialists in general medicine. Some peculiar clinical characteristics of multibacillary, especially lepromatous disease and its systemic involvement23–25 are listed in Table 2; they are often not recognized as HD. Patients with diffuse lepromatous HD, Lucio’s Leprosy, also called Lucio-Alvarado-Latapi form of HD or Lepra bonita, may have diffuse and discrete infiltration with loss of body hair but no visible skin nodules. Other clinical manifestations may be rhinitis, alopecia, telangiectasia of face and chest, facial acne rosacea and livido on the lower limbs.25,26 A study from Brazil of uncommon HD presentations discusses a patient who was initially diagnosed as suffering from systemic lupus erythematosus with erythema and telangiectasia in the face, fever, Reynaud’s phenomenon and significant weight loss.27 In the same article, a patient with Sweet’s syndrome is presented who later on turned out to have HD.

Particular features of HD may mimic rheumatic diseases. A study from the Division of Rheumatology, University of California Medical Centre of 1980 mentions that 15 out of 21 of their HD patients displayed a broad range of rheumatic manifestations.28 Often, such patients with rheumatic disease are only then correctly diagnosed when they develop cutaneous ENL.29,30 A study from Los Angeles, USA on ‘Erythema nodosum leprosum – ENL – in a general hospital’ reports that out of the 22 patients who presented with ENL before the start of chemotherapy and were not previously diagnosed, 5 (23%) of them had no obvious signs of lepromatous HD.31 Opromolla mentions in 1981 that in some lepromatous patients, the first sign of the disease may be erythema nodosum.32

Another uncommon manifestation is the EM-like of ENL. The presentation of a type 2 reaction resembling EM as the first manifestation of HD has been described more than once.27,33,34 Santa Casa, being a teaching hospital, has a protocol in the dermatology department which states that all patients presenting with EM-like lesions should have a skin smear taken for HD. In general, it is considered that the EM-like form of ENL and Lucio’s Leprosy are rarely seen outside Latin America.

There is ample literature prior to the introduction of effective anti-HD treatment discussing initial symptoms and signs of HD, such as rhinitis, before the appearance of the more well-known signs of HD.35,36 It is typical for the evolution of HD involving the upper respiratory tract to start with the involvement of the nose.25

In the differential diagnosis of chronic nasal obstruction in endemic areas, HD has to be considered.37 In 1934, Dr Rabelo Filho (Rio de Janeiro, Brazil) described a patient with a history of recurrent ulcerations of the legs for 4–5 years. Neither nerve involvement was found, nor typical HD lesions, like macules, nodules or gross infiltration.38 Ulceration of the lower legs can develop before the onset of the more typical lepromatous lesions.39 Such ulcers do not react to the usual treatment, but heal rapidly when anti-HD treatment is started. These ulcers should be differentiated from those of Lucio’s phenomenon, necrotic cutaneous vasculitis.40 In HD, oedema of the lower legs, mostly bilateral and more evident in the evening, may precede by months or even years the appearance of the more typical skin lesions.25,41 This phenomenon is different from oedema of face, hands and/or feet that can happen in HD in the context of reactions.42

There are several case reports mentioning lepromatous lymphadenopathy masquerading as other diseases, such as lymphoma.43 In several textbooks, leukaemia and lymphomas are mentioned in the differential diagnosis of LL disease.25,43 Lymphadenopathy in HD is usually associated with episodes of reaction, especially in LL disease. There may even be purulent discharge from the nodes, a condition mimicking tubercular
lymphadenitis.\textsuperscript{24} Lymphogranuloma venereum is mentioned in a study from Brasil.\textsuperscript{44} Those findings should be considered atypical and are mostly only confirmed to be HD by the pathologist. However, with a careful dermato-neurological examination, even in such cases, the suspicion of HD could be raised and the diagnosis confirmed.\textsuperscript{37}

**Conclusion**

There is no human infectious disease in which the clinical picture is as varied as in HD.\textsuperscript{46} In any patient with non-healing skin lesions, treated for a skin disease, particularly when having neurological deficits, living or having lived in an endemic area, the possibility of HD should be considered. It is not so that most patients do not have clear signs or symptoms of HD; it is that most clinicians only pay attention to the more obvious signs or symptoms in his or her own field of expertise, without being aware of the systemic involvement of HD. Special attention should be given to the more uncommon presentations of HD, which are often not recognized in the early stages of the disease. Therefore, referral and support services will continue to play an important role in HD management and control, treating complications, referral and support services will continue to play an important role in the teaching of HD and in the training of health professionals and other health service staff. Due to the increase in global travel and immigration, doctors in low endemic areas also need to know how to identify HD.

**Acknowledgements**

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