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Evaluation of agreement between clinical and histopathological data for classifying leprosy

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SUMMARY

Background: The diversity of clinical manifestations of leprosy has given rise to different classification systems. However, there are important differences in the sensitivity and specificity of these classifications. The objective of this study was to evaluate the agreement between clinical and histopathological data for classifying leprosy.

Methods: A total of 1265 patient reports containing clinical and histopathological data relating to the diagnosis and classification of leprosy were included in this study. The diagnostic concordance between the clinical form (Madrid classification) and the histopathological type, as well as the initial and final classifications, was calculated by dividing the number of concordant cases by the total number of patients.

Results: The overall agreement between the World Health Organization operational classification and the results of direct smear examination of the lesion for acid-fast bacilli was 84.8% (1073/1265). The clinical–histopathological agreement was 58.1% (735/1265). The indeterminate and lepromatous forms were those that showed the highest percentages of agreement: 72.1% (186/258) and 71.0% (142/200), respectively.

Conclusion: Although classifications based on clinical characteristics have an important role in the control of leprosy, they present flaws that can influence the adequacy of treatment. Therefore, a histopathological examination is important for appropriate treatment.

1. Introduction

Leprosy is a chronic infectious granulomatous disease with a prolonged incubation period that affects the skin and peripheral nerves. It is caused by *Mycobacterium leprae*, which parasitizes macrophages and Schwann cells.[1,2]

Annually, approximately 200 000 people are affected throughout the world. The highest detection rates are found in developing countries located in Southeast Asia, Africa, and South America. In 2010, Brazil was the country with the second highest number of cases in the world, only behind India.[3]

Leprosy has a variety of clinical, microbiological, and pathological findings, and it is diagnosed based mainly on the presence of skin lesions, loss of sensitivity, and neural thickening. The various clinical presentations are determined by the different levels of cellular immune response to *M. leprae*,[1,2,4] which are expressed through different pathophysiological mechanisms, with particular signs, symptoms, progression, prognosis, and contagion that have allowed numerous classifications. However, these classifications present important differences regarding sensitivity and specificity, and thus require critical analysis for their application, especially in regions that are considered endemic.[5,6]

The classification proposed by Rabello at the International Leprosy Congress in Madrid in 1953, took into account clinical data and the characteristics of skin lesions presented by patients by dividing them into spectral forms: indeterminate (I), tuberculous (T), dimorphic (D), and lepromatous (L).[7,8]

In 1966, Ridley and Jopling introduced a classification system based on histopathological findings and on the level of cellular immunity.[9] From these criteria, leprosy patients were divided into five groups: tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and lepromatous

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(LL). The indeterminate form (I) included cases that did not fit into any of the five groups.[10]

For treatment purposes, the World Health Organization (WHO) recommends the 'operational classification', based on the number of skin lesions and/or affected nerve trunks. This is recommended because many countries lack the resources required to conduct good quality direct smear examinations for acid-fast bacilli. According to this classification, leprosy cases are considered paucibacillary with up to five skin lesions and/or only one affected nerve trunk, and are considered multibacillary with over five skin lesions and/or more than one affected nerve trunk.[11,12] However, if the direct smear microscopy test is available, patients who present positive dermal smears will be classified as multibacillary, regardless of the number of skin lesions.[13–15]

A correct classification makes it possible to institute appropriate treatment and decreases the transmission of the disease, as well as the chances of recurrence, physical disability, and deformity.[5,7,8,15,16] Deformities can bring problems like reduced ability to work and limitations in the person's social life, and are responsible for the stigma and prejudice against this disease.[13,16]

However, studies have shown that difficulties in establishing the correct classification exist, and have also demonstrated a lack of concordance between the clinical and histopathological classifications.[8,17–19] Furthermore, the simplified criteria adopted by the WHO are not predictive of the correct immunohistopathological classification, which raises the need for a clinical diagnosis accompanied by direct smear microscopy and histopathological examination of the lesion, especially in endemic regions.[7,8,15,20,21]

Hence, the aim of the present study was to evaluate the agreement between the clinical and histopathological data for classifying leprosy.

2. Materials and methods

This was a descriptive retrospective study, with a quantitative approach, based on the analysis of skin biopsy reports from patients presenting clinical and histopathological data concordant with a diagnosis of leprosy, who attended between January 1985 and December 2005. All the reports are filed at the Prof. Dr. Nestor Piva Memorial (PDNPM) facility of Tiradentes University (UNIT).

Out of the 2102 reports involving a histopathological diagnosis of leprosy, 1265 were included in this study because they presented a full clinical summary that indicated a suspicion of leprosy. The information contained in these reports was organized using a specific questionnaire, and the following were thus identified: clinical suspicion relating to the operational classification, clinical suspicion relating to the Madrid classification, direct smear microscopy of the lesion, and histopathological classification.

All the information obtained was coded and entered into a database. An exploratory analysis was conducted on the data, consisting of calculating simple, absolute, and percentage frequencies for the categorical variables and organizing the results into tables through descriptive analysis and associations between variables.

Table 2
Agreement between clinical and histopathological classifications for patients with leprosy; PDNPM, 1985–2005

Clinical classification[a]	Histopathological classification[b]				Agreement, *n* (%)	Total
	I	TT	BB[c]	LL		
I	186	55	11	6	186/258 (72.1%)	258
T	212	375	24	35	375/646 (58.0%)	646
D	36	51	32	42	32/161 (19.9%)	161
L	17	26	15	142	142/200 (71.0%)	200
Total	451	507	82	225	735/1265 (58.1%)	1265

Kappa = 0.371, $p = 0.000$.
[a] I, indeterminate; T, tuberculous; D, dimorphic; L, lepromatous.
[b] I, indeterminate; TT, tuberculoid; BB, mid-borderline; LL, lepromatous.
[c] BB = includes BT (borderline tuberculoid), BB, and BL (borderline lepromatous).

The diagnostic concordance between the clinical form (Madrid classification) and the histopathological type, as well as the initial and final classifications, was calculated by dividing the number of concordant cases by the total number of patients. The kappa test was applied to evaluate the concordance results. The kappa values and their interpretations were as follows: <0, no agreement; 0–0.19, very weak agreement; 0.20–0.39, weak agreement; 0.40–0.59, moderate agreement; 0.60–0.79, substantial agreement; and 0.8–1.0, excellent agreement.[22] The significance level used for the analyses was 5% ($p < 0.05$).

3. Results

Out of the 1265 patients included in the study, 933 (73.8%) presented a clinical suspicion of paucibacillary leprosy and 332 (26.2%) of multibacillary leprosy. From direct smear microscopy performed on the lesion, 67 (7.2%) of those classified as paucibacillary cases were positive and were reclassified as multibacillary, and 125 (37.7%) initially suspected of being multibacillary cases were negative and were reclassified as paucibacillary.

Meanwhile, among those initially classified as paucibacillary cases, 866 (92.8%) were negative on smear microscopy, and 207 (62.3%) initially classified as multibacillary patients were positive on smear microscopy. The overall agreement between the initial and final operational classifications was 84.8% (1073/1265), which was considered moderate (kappa = 0.584, $p = 0.000$) (Table 1).

Table 2 shows the evaluation of the concordance between the clinical classification (diagnostic suspicion) and histopathological classification of the 1265 patients. The data analysis showed an overall agreement of 58.1% (735/1265), which was considered weak (kappa = 0.371, $p = 0.000$). The indeterminate and lepromatous forms were those with the highest percentage agreements: 72.1% (186/258) and 71% (142/200), respectively. The tuberculoid form presented agreement of 58.0% (375/646) and the intermediate forms (dimorphic) presented the lowest agreement, of 19.9% (32/161).

On the other hand, the histopathological examinations of skin biopsies in 41.9% (530/1265) of the patients showed changes to the

Table 1
Agreement between the initial and final operational classifications after direct smear microscopy on the lesion; PDNPM, 1985–2005

Initial operational classification	Final operational classification (direct smear microscopy)		Agreement, *n* (%)	Total
	Paucibacillary	Multibacillary		
Paucibacillary	866	67	866/933 (92.8%)	933
Multibacillary	125	207	207/332 (62.3%)	332
Total	991	274	1073/1265 (84.8%)	1265

Kappa = 0.584, $p = 0.000$.

leprosy classification, and 20.2% of them (256/1265) changed from one pole of the spectrum to the other.

4. Discussion

The correct classification of leprosy cases is an important tool for the proper allocation of patients in the multidrug therapy (MDT) program, since the duration of treatment and dosage of medication used differ between the paucibacillary and multibacillary forms.[14]Accordingly, evaluation of the agreement between classification systems using clinical criteria and those based on laboratory tests have been a frequent focus of studies over the last few years,[6] especially since the publication of the WHO operational classification, which recommends that the sole criterion for classifying patients should be the number of skin lesions, with allocation into two different therapeutic regimens.[14] Studies have shown that the use of this classification method alone, in routine practice within healthcare services, presents limitations and different percentages of sensitivity and specificity.[5,6,23–25]

In the present study, the general agreement between the initial and final operational classifications was 84.8%. Other studies have shown concordance ranging from 83.1% to 89.3%.[5,8,25] The lowest agreement was among multibacillary patients, which shows the need to conduct smear microscopy, in order to increase the rate of diagnosis.

It was found that smear microscopy on the lesion changed the classification in approximately 15% of the cases. Teixeira et al.[8] evaluated the agreement between the WHO operational classification and the smear microscopy index for lymph and demonstrated that smear microscopy changed the diagnosis in 5% of the cases. This lack of agreement between the data of the present study and the data of Teixeira et al.[8] can be explained by the fact that direct smear microscopy on the lesion makes it possible to find bacilli in the deep reticular dermis, where bacilli remain inaccessible to lymph smear microscopy.[26] Bhushan et al.[20] evaluated the agreement between lymph and slit-skin smear microscopy, and found that the smear microscopy of the lesion identified more multibacillary patients. These authors concluded that smear microscopy of the lesion has a greater sensitivity and specificity and should be done routinely, when available, for classifying patients.

The results from the present study showed that 67 (7.2%) of the paucibacillary cases were reclassified as multibacillary. This error in classifying patients may represent a situation of inadequate treatment that consequently increases the risk of recurrence and the period for which the patient would continue to be a source of infection, due to under-treatment. On the other hand, 125 patients (37.7%) who were initially classified as multibacillary were negative on smear microscopy, thus indicating that they would be unnecessarily subjected to treatments that could potentially result in serious adverse effects and increase the spending on healthcare services.[5]

The agreement between the clinical suspicion according to the Madrid classification and the histopathology of the lesion was 58.1%. Other authors have reported percentage agreements ranging from 29.7% to 89.0%.[8,17–20,27–32] The greatest agreements have occurred with the polar forms and the smallest rates with the intermediate forms (dimorphic).[8,20,21]

It was found that the histopathological analysis significantly changed the classification of the patients in 20.2% (256/1265) of the cases, i.e. they moved from one pole of the spectrum to the other. This was because patients histopathologically classified as I, TT, and BT were treated as paucibacillary, and those diagnosed as BB, BL, and LL received the therapeutic regimen for multibacillary.[14] Therefore, the importance of complementary laboratory tests to help in diagnosing and correctly classifying leprosy is emphasized.[21]

Because of the wide spectrum of clinical manifestations of leprosy, studies have shown the importance of using histopathological criteria among patients with leprosy, and correlating results with the clinical diagnosis, in order to improve the classification of the patients, as well as the prognosis and treatment.[8,20,21,33,34]

In conclusion, the analysis in this study showed moderate agreement between the operational classification based on the WHO and operational classification based on smear, and weak agreement between the Madrid classification and pathology. The findings suggest that for a correct classification of the forms of leprosy and thus for the institution of appropriate therapy, histological examinations of the lesion should be performed, associated with clinical signs of the disease.

Ethical approval: This research was approved by the Ethics Committee of the Universidade Federal de Sergipe (Brazil); CAAE protocol 0038.0.107.000-11.

Conflict of interest: No conflict of interest to declare.

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