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Primary neural leprosy: systematic review

Hanseníase neural primária: revisão sistemática

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ABSTRACT

The authors proposed a systematic review on the current concepts of primary neural leprosy by consulting the following online databases: MEDLINE, Lilacs/SciELO, and Embase. Selected studies were classified based on the degree of recommendation and levels of scientific evidence according to the "Oxford Centre for Evidence-based Medicine". The following aspects were reviewed: cutaneous clinical and laboratorial investigations, i.e. skin clinical exam, smears, and biopsy, and Mitsuda's reaction; neurological investigation (anamnesis, electromyography and nerve biopsy); serological investigation and molecular testing, i.e. serological testing for the detection of the phenolic glycolipid 1 (PGL-I) and the polymerase chain reaction (PCR); and treatment (classification criteria for the definition of specific treatment, steroid treatment, and cure criteria).

Key words: leprosy, neuropathy, systematic review, diagnosis.

RESUMO

Os autores propuseram-se a realizar uma revisão sistemática em conceitos atuais sobre a hanseníase neural primária, consultando as seguintes bases bibliográficas *on-line*: MEDLINE, Lilacs/SciELO e Embase. Os estudos selecionados foram classificados conforme o grau de recomendação e o nível de evidência científica de acordo com o "*Oxford Centre for Evidence-based Medicine*". Os seguintes temas foram revisados: investigações clínica e laboratorial cutâneas, ou seja, exame, esfregaço e biópsia de pele e reação de Mitsuda; investigação neurológica (anamnese, eletroneuromiografia e biópsia de nervo); investigação sorológica e testes moleculares, ou seja, testes sorológicos para detecção de um glicolipídio fenólico e reação de cadeia de polimerase (PCR) e tratamento (critérios de classificação para definição de tratamento específico, tratamento com esteroides e critérios de cura).

Palavras-Chave: hanseníase, neuropatia, revisão sistemática, diagnóstico.

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This study is a systematic review on the current concepts of primary neural leprosy (PNL). The following online databases were consulted: MEDLINE, Lilacs/SciELO, and Embase. Selected studies were classified based on the degree of recommendation and levels of scientific evidence according to the "Oxford Centre for Evidence-based Medicine".

In an editorial of the International Journal of Leprosy, Wade[1](D) mentioned the results of the International Symposium on the Leprosy Classification, which recognized the polyneuritic form of leprosy.

The assessment of 20,000 patients with leprosy, from five continents, during a 28-year-period, showed that neuritic manifestations, mainly specific paresthesia, are common, being presented as mononeuritis or multiple mononeuritis, which may precede cutaneous lesion in several months[2](C).

Therefore, suspected of PNL are those patients that present single or multiple mononeuropathy and polyneuropathy (confluent mononeuropathies) as a first manifestation of leprosy, without other identified etiology and skin lesions.

PREVALENCE

PNL prevalence is low, but it can be overestimated when the investigation of the skin lesion is not complete[3,4](C), as well as when there is no adequate differential diagnosis[4](D).

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An epidemiologic study carried out in India followed 8,000 individuals during five years. Eight hundred patients were identified with leprosy, being 106 cases of PNL. The annual incidence was of 8.2:1000[5](C).

Dongre et al.[6](C), also in India, studied 11,581 individuals, and found 494 PNL cases (4.3%) and 143 (1.2%) with specific nonvisible anesthetic lesions, totalizing 5.5% of patients without visible skin lesions.

There are no similar data in Brazil, but in one reference center from São Paulo State, including 162 patients that underwent nerve biopsy between 1985 and 2005, 34 cases of PNL were diagnosed, that is, less than two per year[4](D).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis should target causes for mononeuropathy and multiple neuropathy, including inflammatory (collagenosis and non-systemic vasculitis); metabolic (diabetes, hypothyroidism and dysfunction of the hypophysis); infectious (syphilis and Aids); traumatic and postural (acute and chronic compressions); congenital or hereditary (syringomyelia/syringobulbia, congenital insensibility to pain, hereditary neuropathy with susceptibility to pressure), and tumoral (neural sheath tumors and others) ones. The histopathological analysis of the nerve must be able to generate parameters to establish likely diagnosis[4](C).

OBJECTIVE

The aim of this review was to elaborate recommendations and standardizing procedures towards the diagnosis of PNL, based on scientific evidences.

DIAGNOSIS

Clinical investigation of the primary neural leprosy suspected cases

In PNL, there is absence of cutaneous lesions, and slit skin smear of suspected areas can also be negative for *M. leprae*. Follow-up of 182 PNL cases along 36 months showed that 29 patients (15.8%) developed skin lesion[7](C).

Peripheral neuropathy may precede skin lesions from 15.0 to 35.0% of PNL cases[7,8](C). Follow-up of such patients is always necessary[9](C) because leprosy reaction may appear on many of them, redefining the diagnosis[10](C).

If there is clinical suspicion of PNL, detailed dermatological assessment and follow-up should be done even after starting the specific treatment for leprosy. Onset of reaction or skin lesion confirms the diagnosis and reclassifies the form of leprosy, consequently helping on the prevention of nerve damages.

Diagnosis value of the skin bacilloscopy on suspicion of primary neural leprosy

Patients that are suspected of PNL show peripheral neuropathy, without other likely etiology and skin involvement clinically nor laboratorially identifiable[1,4,10](D). For example, in a series of PNL suspected cases studied between 1991 and 2004, only patients with negative skin bacilloscopy were included[11-13](C). Indeed, this is fundamental even in the absence of visible skin lesions, as well as the bacilloscopy index (BI)[14](D). The areas where bacilli are most likely to be found are the cold regions of the skin: ear lobes, posterior region of the elbows and anterior one of the knees, where loss of sensitivity is more frequent[15](B). It is however important to note that bacilloscopy is positive only after a load 10^4 bacilli/gram of tissue is reached. In this sense, false negative smears can be expected in borderline patients[16](C).

The BI study must be conducted on the ear lobes, posterior region of the elbows and anterior one of the knees, before directing the patient to reference centers or specialized consultation. When the BI is greater than zero, the PNL diagnosis is invalidated and classified as multi-bacillary leprosy.

Value of the skin biopsy on the primary neural leprosy diagnosis

The diagnosis confirmation of the PNL is challenging, once two cardinal signs of leprosy (skin lesions and smears for acid fast resistant bacilli) are absent.

In 208 patients with PNL confirmed after neural biopsy, the cutaneous one was performed on hypo/anesthetic areas (133 patients) and on preserved sensitivity regions, near to the affected nerve (63 patients), founding compatible histopathological alterations on 58.6% of the cases. Also considering the non-specific inflammatory alterations, the positivity rose to 81.1%. The sensitivity for nerve biopsy (75.9%) is greater than that for skin biopsies (58.6%), even though the latter is less invasive[17](B). Some authors did not found histopathological alterations on the anesthetic areas without skin lesions[11](B), while others demonstrated that the skin biopsy of such areas was abnormal from 31.0 to 33.3% of the cases[13,18](C), reaching up to 64% when the non-specific inflammatory alterations were also considered[18](C).

In suspected cases of PNL, skin biopsy on hypoesthetic areas may help the diagnosis; however, in their absence, cutaneous biopsy on the regions near the affected nerve may help the diagnosis. The absence of cutaneous alterations in the histology does not exclude the diagnosis. As it is less invasive than the neural, skin biopsy is recommended as the first option.

Interpretation of Mitsuda's test and its meaning in primary neural leprosy diagnosis

Mitsuda's test is performed with an intradermal inoculation of a solution of killed by heat *M. leprae* bacilli. Reading

is done after four weeks, being positive if there is a papule greater than 5 mm or ulceration. The histopathology may show granulomatous reaction similar to the tuberculoid form[19](C). Most populations in endemic areas present positive responses, not getting sick, or can develop the tuberculoid form, which is not transmissible[20](B). Therefore, Mitsuda's test helps in the classification and prognosis[21](B).

In a population with 137 individuals with PNL, who undergone Mitsuda's test investigation, it was observed that 93 (70%) of those presenting positive reaction to such evaluation, only 16 were borderline lepromatous (BL) or lepromatous (LL) on the histopathology from the damaged cutaneous nerve or skin with sensory impairment. Out of 44 (30%) individuals with negative test, 28 (64%) were LL or BL on histopathology. Mitsuda's test must be judiciously used to classify PNL in paucibacillary (PB) or multibacillary (MB)[17](B), along with the clinical and histological findings. Isolated, the test is not useful for the PNL diagnosis[18](C).

In case of neuritis in patients with PNL, the positivity of the test ranges from 57.1 to 100.0%[13,22](C). The positivity of Mitsuda's reaction in 5 LL/BL cases reinforces the need for the histological analysis of the reaction[23](C). Though being of a poor diagnostic value, Mitsuda's reaction is useful for assessing on the immunological and prognostic status[23](C). Subjects with positive Mitsuda's test and low antibodies titles usually correspond to the tuberculoid form (TT) or borderline-tuberculoid (BT), while those with negative and high antibodies titles correspond to the MB Group. The test shows higher indurations diameter in PB patients[23](C).

Mitsuda's test, together with the clinical, serological, and histopathological data, helps in the operational classifications of patients with PNL.

Neurological manifestations of leprosy

The assessment of the patient with PNL must follow the same steps of that with multiple mononeuropathy, and the neurological approach must be as wide as possible.

Van Brakel and Khawas[24](B) studied 396 new cases, finding motor function impairment in 96 and sensory impairment in 116. The most common damages were the sensory component of the posterior tibial (21.0%), motor component of the ulnar (20.0%), sensory component of the ulnar (17.0%), sensory component of the median (8.8%), and motor component of the lateral popliteal (4.8%).

Ramadan et al.[25](C) assessed 40 patients, being the ulnar nerve the most frequent damaged and the claw hand the most common disability. All the sensory modalities were affected: superficial and deep sensitivities. However, deep pressure was altered only on late cases. The sensory impairment predominated over the motor.

Jardim et al.[26](C) assessed 49 patients with PNL, observing paresthesias in 55.0%, motor impairment in 24.0%, neural pain in 12.0%, and sensory loss in 8.0%. Multiple mononeuropathy was observed in 61.0%, mononeuropathy in 33.0% and only three patients (6%) presented polyneuropathy. Sensory nerves were more compromised than the motor ones, and the ulnar nerve was the most frequent affected.

Van Brakel et al.[27](B) assessed 303 patients with leprosy, observing good concordance between the monofilament and the other tests of sensory function, validating the monofilaments as the standard form of screening. Heat sensitivity was more accurate than the cold, and there was a positive correlation to the touch.

Jardim et al.[28](C) studied 19 patients with PNL, and clinically they found sensory and motor losses in 78.9% of the cases, followed by neural thickening (68.4%) and pain (42.1%). In other study, Jardim et al.[29](B) assessed 24 patients with PNL. The main manifestations were sensory (21/24), predominating paresthesias (17/21), pain (2/21) or hypoesthesia (2/21). On three patients, the initial manifestation was motor, being amyotrophy in one of them and muscle weakness in the others. In the first exam of these patients, before treatment, the following were observed: acrocyanosis (71.0%), neural thickening (21.88%), muscle weakness (88.0%), and sensory impairment (83.0%).

Dos Santos[15](B) analyzed 20 patients with leprosy, and observed that the sensory loss predominated on the following regions: posterior of the elbow, posterior of the forearm all the way to the back of the hand, on the palm of the hand, on the knee, and on the side strip of the leg down to the distal region on the foot and plantar region. The posterior region of the elbow, specially, had high diagnostic value. The sensitivity to pain was involved earlier, being more extensive than the tactile one. The author concluded that the sensory loss in leprosy has a pattern of preferential topographic distribution that contributes to the characterization and diagnosis of such neuropathy[15](B).

Existing data is contradictory, and the methodology and objective of the studies are heterogeneous. Seemingly, the neuropathy of the PNL has a predominantly sensory involvement. Sensitivity to heat and pain are the most compromised, and in general, it has an asymmetric pattern of multiple mononeuropathy. The nerves with higher frequency of impairment, in the analyzed series, were the ulnar, the superficial radial, the sural, the superficial fibular, and the tibial in the sensory modality. The less frequently involved nerves were the common fibular and median.

Nerve conduction studies: diagnostic of sensibility and specificity

During the course of the disease, a patient with leprosy neuropathy may present many physiopathological processes in different periods, depending on the clinical classification, evolution, and treatment. In this connection, nerve conduction studies (NCS) are a sensitive method for the investigation of PNL[13,28,30](C). The most common pattern observed is

the multiple mononeuropathy (79.0%), with occurrence of isolated mononeuropathy (10.5%) or distal polyneuropathy (10.5%)[28](C). The Program of the International Federation of Anti-Leprosy Associations (ILEP) denominated ILEP Nerve Function Impairment in Reaction (INFIR) assessed 268 patients with positive bacilloscopy or at least six skin lesions, and it was observed reduction of: sensory nerve action potential (SNAP) amplitudes (sural 65.0%, radial 57.0%, ulnar 40.0%, and median 36.0%); sensory conduction velocity (sural 49.0%, radial 34.0%, ulnar 25.0%, and median 21.0%); compound motor action potential amplitudes — CMAP (fibular 34.0%, median 25.0%, and ulnar 23.0%): and motor conduction velocity (ulnar 36.0%, fibular 16.0%, and median 15.0%)[31](B). Another study from India, with 357 patients, presented alterations on sensory nerve conduction in 88.0% and on motor conduction in 75.0%[32](C).

Andrade[33](C) assessed 77 cases of leprosy with neuropathy. The most prevalent pattern was the asymmetric sensory-motor neuropathy in 61.0%, with focal reduction of conduction velocity; 19.0% presented asymmetric and axonal sensory-motor neuropathy, without focal reduction detected; and 12.0%, asymmetric sensory-motor neuropathy, with predominance of sensory onset. Capadia et al.[34](B) detected neurophysiologic alterations on the 21 patients with PNL, and 18 presented sensory-motor abnormalities. Other studies have confirmed such findings[25,35-37](C). There is prominence of demyelinating neuropathy of the ulnar nerve at the elbow in 55.0% of the cases[34,36](C). All these studies emphasize the asymmetric and multifocal impairments.

The neurophysiological evaluation is more sensitive than the clinical examination for the detection of nerve impairment[31](B),[38](C), and the presence of abnormalities is frequent, even on nonenlarged nerves[37](C). Patients without clinical involvement presented abnormalities on NCS in 40.0% of the cases[38](C).

Though the needle electromyography expands the information obtained by NCS, there is no evidence that this technique increases the sensitivity of the test[38](C).

Besides the strictly diagnostic aspects, NCS are useful on the follow-up, mainly in patients with types 1 and 2 reactions[39](C). NCS are abnormal even earlier than the threshold of heat sensation[40](B). While evaluating the distribution of the neuropathy, NCS also help in choosing the nerve to be biopsied[13](C).

The NCS should be performed on patients with suspicion of PNL, in order to characterize the neuropathy and help with the choice of the nerve to be biopsied. During and after treatment, they help in the follow-up of the neuropathy and diagnosis of acute or subacute reactions on nerves.

Sensibility and specificity of the serological testing for the detection of phenolic glycolipid 1 antibodies

The phenolic glycolipid 1 (PGL-1) is *M. leprae* specific. Antibodies, mainly the IgM class, are useful for the evaluation of infection, and its level shows a strong correlation with the bacillary load[41](C). They are detected by enzyme assay (ELISA), passive hemagglutination test (PHA), hemagglutination on gelatin particle (MLPA) and rapid tests for field use, such as ML-Flow, which demonstrated 91% of concordance with the ELISA method (95%CI 0.70–0.84)[42](B).

Additionally, the ML-Flow test showed positive results in 97.4% of MB patients; 40.0% on PB, 28.6% on household contacts, and 9.8% in the Control Group. Therefore, the sensibility of the test related to the correct classification of the patients was 97.4% for MB. The specificity of the method, based on Control Group results, was 90.2%[42](B).

At a recent systematic review, it was mentioned a 78.0% average sensibility for MB patients, though 23% of PB and also apparently healthy contacts may present positive serology on low levels[43](B), demonstrating that the test may help in the classification of patients, correlating with antibody level and bacteriological index. In this review, there was no significant difference between the ELISA test and the rapid methods of antibodies detection. The positivity of the tests becomes higher with the increase on the number of affected nerves and skin lesions.

The serology may also be useful in the follow-up of neuropathy and in monitoring MB patients' treatment as well as individuals under relapse risk. Subjects with more than one compromised nerve trunk have four times greater chances to be seropositive (OR=2.4), even with few or no cutaneous lesions[44](B).

The antibody levels are significantly higher on patients with leprosy than on the Control Group[45](C).

In another study, the results of the IgM anti-PGL-1 antibodies tested by ELISA were compared on four populations: nontreated patients, MB subjects treated for 12 months with multidrug therapy (MDT), MB ones treated for 24 months with MDT, and PB individuals treated for six months with MDT. Statistically significant differences were found ($p<0.01$) in the IgM anti-PGL-1 values: between nontreated patients and the MB patients treated for 12 months (6.95±1.35 *versus* 2.78±0.69), and between the nontreated patients and MB ones treated for 24 months (12.53±2.02 *versus* 2.62±0.79). There was no significant difference between nontreated patients and PB treated ones[46](B). These data indicate that the monitoring of anti-PGL-1 levels during MDT may be a sensitive instrument for the evaluation of the treatment efficacy.

The serology for IgM anti-PGL-1 detection is useful for evaluating the *M. leprae* infection level and monitoring the bacillary load. However, it should not be the only criterion for the diagnosis of leprosy, as it can be false negative in some MB cases. Additionally, on endemic areas, this technique makes no distinction between infection and disease. Patients diagnosed with leprosy with titers higher than 0.15 on ELISA ND-O-BSA (natural disaccharide – octyl – bovine serum albumine) should be treated with MDT for MB patients.

Nerve biopsy on primary neural leprosy

The sensibility of neural biopsy (75.9%) is greater than skin biopsy (58.6%), although the nerve one is quite invasive[17](B). Some authors have demonstrated that skin biopsy of areas with sensory alteration present histopathological evidences of leprosy at a proportion that varies from 31.0 to 50.0%[18,26,28](C), reaching up to 64.0%, if nonspecific inflammatory alterations are considered[18](C).

Sixty-seven patients with PNL underwent biopsy of the dorsal cutaneous branch of the ulnar, sural, and superficial fibular nerves; 16.0% of them evidenced bacilli alcohol acid resistant (BAAR) and the molecular diagnosis based on the biopsy was positive in 47.0%[26] (C).

A total of 33 patients suspected of PNL were followed clinically from 1994 to 2004. All of them underwent nerve biopsy, 29 sural nerves and four dorsal cutaneous branch of the ulnar nerve. The biopsy confirmed leprosy in 11 patients (33.3%)[13] (C).

In 19 patients with PNL and nerve biopsies, morphological alteration was found in all biopsied nerves, although BAAR was found only in three cases. In six people, molecular diagnosis was made by the polymerase chain reaction (PCR)[28] (C).

In one subject with superficial fibular neuropathy, the diagnosis was made based on the presence of BAAR on the biopsy of such nerve[47](C).

One male patient presented multiple floating saccular formations in the subcutaneous region on the projection of several nerves. The biopsy exam of the superficial radial nerve lead to the diagnosis of BT leprosy, based on granulomatous infiltrate of epithelial cells, lymphocytes and caseous necrosis, that is, a nerve abscess[48](C).

Cases with clinic-neurological and/or electrophysiological evidence of PNL may have an indication for nerve biopsy. It must be performed exclusively on sensory nerves or their branches with unequivocal impairment. In this context, the sural nerve should be the first choice.

Histopathological patterns found on nerve biopsy and the indication of semi-thin section

On the histopathological study of the nerve, the hematoxylin-eosin, the Faraco-Fite and the immunohistochemistry, which is the anti-BCG antibody[13](C), are the routine staining techniques. The evaluation of the histological sections may show the same patterns of leprosy observed on skin lesions, as well as an unspecific framework, which include: discrete chronic inflammatory infiltrate, nongranulomatous, epi, peri and endoneurial fibrosis, and hyalinization of the nerve. Bacilli or bacterial antibodies may also be detected on Schwann's cells or inside endoneurial granulomas. On late stages, it is possible to observe an extensive fibrosis and hyalinization of the endoneurium and a complete destruction of the nerve architecture[13,26,28] (C).

The microscopy of semi-thin sections (0.5 μm thick) shows the reduction of the number of large and small myelinated fibers, demyelination, axonal degeneration, besides allowing greater accuracy in the visualization of the sub-perineurial edema and thickening of perineurium. However, it is not more sensible than the staining of Fite-Faraco for BAAR detection. The microscopy of semi-thin sections does not increase the sensitivity of diagnosis of specific leprosy alteration, but it contributes to detect unspecific alterations, helping with the differential diagnosis[28](C).

The samples histopathology of hypoesthesic skin areas of patients with PNL, particularly on regions supplied by clinic or electrophysiological impaired nerves, may show the presence of perineurial inflammatory infiltrate around cutaneous nerve filament in 31.0% of the cases, which confirms the diagnosis without the need of nerve biopsy[18](C).

The diagnosis of certainty and the very probable diagnosis will be performed when the following aspects are observed: inflammatory infiltrate composed by vacuolated macrophages (Virchow cells), containing BAAR inside macrophages and Schwann cells, accompanied by sparse lymphocytes, and granulomatous inflammatory infiltrate with epithelioid cells, occupying the endoneurium and absence of BAAR on biopsy. The probable and possible diagnoses will show: lymphocytic and macrophagic inflammatory infiltrates without differentiation for epithelioid cells, not even for Virchow cells, occupying the endoneurium around vessels permeating nerve fibers and absence of BAAR, and epi, peri and endoneural fibrosis, edema of the subperineurial space with an increase of the mononuclear lymphocytic cells (lymphocytes and macrophages). Such findings may be accompanied by a numeric loss of large and small myelinated fibers.

Nerve biopsy must always be indicated when there is suspicion of PNL without other confirmatory findings by other exams. Semi-thin sections study is a supporting procedure allowing the detection of unspecific alterations that can strengthen the diagnosis of possibility and help in differential diagnosis.

Diagnostic value of polymerase chain reaction

There are few studies regarding the diagnostic value of PCR. Martinez et al.[49](B) amplified the 85 kDA gene in 69 samples of skin biopsy of leprosy patients. MB patients were all positive, and among the PB ones the detection rate varied from 62.5 to 79.2%. Jardim et al.[26](C) performed PCR on material extracted from nerves and the results were positive in 16 out of 20 BAAR negative patients; among them, four out of 16 had normal biopsy.

Bezerra da Cunha et al.[50](C) studied the PCR on nerve samples of 40 BT and 18 TT patients. Out of 38 BAAR negative biopsies (20 BT and 18 TT), it was positive on 14 (12 BT and 2 TT).

The certainty diagnostic of PNL through histopathology depends on the presence of BAAR. PCR adds sensitivity on BAAR negative cases. It adds sensitivity to routine histological methods. Every nerve sample harvested due to PNL suspicion must have a nonfixed fraction stored in dry ice for PCR study.

TREATMENT

Classification criteria in primary neural leprosy cases to define specific treatment

At the International Symposium for Leprosy Classification in 1952, there was no consensus about PNL. For some, it was a special form of leprosy, for others the matter was considered uncertain[1](D). The Madrid and Indian classifications[10](D) considered that PNL could be within any of the following clinical forms: undetermined, tuberculoid, and dimorphous or virchowian.

The PNL ranking depends on the neurological, immunological, and histopathological findings. It is considered PB when there is only one damaged nerve, and MB when there is more than one[12,51](C).

The immunological evaluation depends on Mitsuda's test and on the IgM anti-PGL-1 serology. In the PB patients that present positive Mitsuda, a negative serology is expected, and for MB, the opposite[10](C), [11,44](B).

Nerve histopathology may define PB (tuberculoid) or MB (borderline-lepromatous, borderline-borderline and borderline-tuberculoid)[13,52](C) forms.

In the absence of histopathological abnormalities on nerve biopsy or of biopsy, the PNL classification should be done on the basis of clinical and immunological criteria, the number of compromised nerves and the result of Mitsuda's reaction.

Cure criteria for primary neural leprosy

The World Health Organization (WHO) recommended that MDT must be given according to the operational classification (PB or MB)[51](D). The patient is released from treatment at the end of the doses prescribed for each group[14]. Some experts believe MDT has the disadvantage of not eliminating the mycobacterial antibodies from the nerves, which may maintain neuritis and cause future disabilities throughout time, even after the patient has been cured. Despite the improvement with MDT, some patients show persisting activity, with reactions and relapse[53](C).

An alternative regimen with dapsone, clofazimine and rifampicin for six months for PB and MB showed a poor response under clinical (35.0 against 77.0% on MDT-WHO) and histopathological points of view (50.0% when compared with MDT preconized by WHO)[54](B).

Relapse is defined by the presence of new signs and symptoms and new BAAR detection on the skin or nerve biopsy. Relapse rate varies between 1.0% and more than 40.0% depending on the treatment regimen, follow-up duration, and if it was determined by physical exam, skin smear, or biopsy[53](C).

The patient with PNL is considered healed after receiving the MDT regimen adequate to the clinical form. However, the individual should be oriented to return if there is worsening of neural function or in the appearance of new skin lesions.

Studies on prophylactic treatment with steroids combined to specific therapy on primary neural leprosy

The preventive treatment of neuritis with steroids together with MDT is still discussed, even in MB forms. In a randomized study, an initial dose of 20 mg/day *versus* placebo was used, and then it was progressively reduced in four months. The authors observed the reduction of new reactions incidence during steroid use and a decrease in the sensory loss. However, these effects did not persist after the interruption of the steroid treatment[55](B).

In a study where an initial dose of 40 mg/day was used and reduced in up to 12 months to 5 mg/day, with repetition of treatment if reactions appeared, it was observed impairment prevention and improvement of motor function during drug administration, but the sensory impairment did not show any function recovery[56](C).

The electrophysiological assessment of 24 PB PNL patients with neural loss, treated with an initial dose of 60 mg/day orally, which was progressively reduced for six months, presented significant sensory and motor improvements in the study period[29](B).

Random clinical trial including 21 MB and PB patients, with electrophysiological follow-up during a six-month treatment period, showed that initial doses of 1 mg/kg/day presented the same effectiveness as the 2 mg/kg/day dosage, if introduced within less than three months after the first symptoms[57](B). The adverse effects were more pronounced when the initial dosage was 2 mg/kg/day.

In cases of PNL there are no evidences on how long reactions will happen after the MDT[58](D). An exploratory cohort study, with 594 MB and PB patients, concluded that MB patients reduce to a third the incidence of reactions in four years after the end of MDT, and PB patients after two years[59](B).

PNL patients must have a follow-up plan during and after MDT, in order to monitor neurological loss, for at least two years considering that most of the patients are PB. Under the presence of active neuropathy, by clinic or by electrophysiology, it is indicated to start treatment with steroids, with doses of 1 mg/kg/day. If this picture is found at the moment of diagnosis, the treatment should be initiated with prednisone, along with MDT.

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