

# Contribution to diagnosis and management of reactional states: a practical approach\*

## *Contribuição ao diagnóstico e manejo dos estados reacionais. Uma abordagem prática\**

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**Abstract:** The early clinical recognition of reactional states brings great benefits to leprosy patients due to the possibility of appropriate and immediate therapeutic intervention, thus avoiding the development of disabilities that so much stigmatize and complicate the disease. There are three types of reactional episodes: types 1, 2 and neuritis. The latter may occur alone or together with the former forms. In some cases only neurological and/or skin manifestations are observed in the reactions; in others, patients present systemic alterations. The treatment with an association of immunosuppressors and anti-inflammatory drugs seems to be the most effective to avoid recurrences and side effects.

**Keywords:** Diagnosis; Erythema nodosum; Leprosy; Neuritis

**Resumo:** O reconhecimento clínico precoce dos episódios reacionais traz grandes benefícios para os pacientes com hanseníase, devido à possibilidade de intervenção terapêutica imediata e adequada, evitando o desenvolvimento de incapacidades que tanto estigmatizam e complicam a doença. Existem três formas de episódios reacionais: os tipos 1 e 2, e a neurite. Esta última pode aparecer isoladamente ou acompanhar as formas anteriores. Em alguns casos só são observadas as manifestações cutâneas e/ou neurológicas das reações, enquanto em outros, alterações sistêmicas podem acrescentar-se ao quadro. O tratamento utilizando a associação de medicamentos antiinflamatórios e imunossuppressores parece ser o mais adequado para evitar as recorrências e os efeitos colaterais.

**Palavras-chave:** Eritema Nodoso; Diagnóstico; Hanseníase; Neurite

### INTRODUCTION

Leprosy would not have major repercussions during its progression if there were not reactional episodes. The aim of this review is to provide theoretical support for improved understanding and management of these episodes to decrease morbidity and clinical consequences.

### CONCEPT

Reactional states are immunoinflammatory events presenting almost always as local or systemic dermatological and neurological manifestations that occur at distinct moments (before, during or after the specific treatment of leprosy) and that require immediate intervention.

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**CLASSIFICATION**

There are three clinical presentations of reactional states. Type I is the reverse reaction (RR) that occurs mostly in patients with borderline tuberculoid (BT), borderline-borderline (BB) and borderline lepromatous (BL) forms.<sup>1</sup> This reaction occurs very seldom in the lepromatous- lepromatous type (LL). Type II, erythema nodosum leprosum (ENL), occurs in patients with LL and BL. A third type of reaction, named isolated neuritis, is a reactional state which presents as pain (spontaneous or promoted by compression of a nerve trunk), accompanied or not by nerve thickening, with no dermatological features of types I or II.<sup>2</sup> Nery et al. found seven cases of isolated neuritis in 100 multibacillary (MB) patients with reactional states. The frequency of isolated neuritis was 57.1% in the BB form, 28.6% in the BL form and 4.3% in LL patients.<sup>3</sup>

**TYPE I REACTION: REVERSAL REACTION**

**Pathophysiology**

Reversal reaction (RR) or type I reaction is an event that follows a sudden development of cell mediated immunity; it is considered a transitory state directed towards the tuberculoid type, sometimes with positive lepromin skin tests and formation of epithelioid granulomas. The presentation may vary with the clinical form (Chart 1). Usually reactivation of preexisting lesions or the appearance of new lesions in previously healthy areas with erythema and infiltration are observed, forming a smooth and bright plaque with an edematous surface, which may regress with scaling and residual hyperchromia. The reactional state may last weeks or months.

The mucosa and semimucosa may also be affected, as well as the skin. A burning sensation in cutaneous lesions, facial or extremity pain, paresthesia, decreased sensitivity and reduced muscular strength may be present.<sup>4,5</sup>

**Clinical variants of the type I reaction**

- Melanodermic patients may present nodules (pseudonodules), mostly on the face, sometimes in other areas, that may be erroneously diagnosed as erythema nodosum.<sup>6</sup>
- Aspect similar to erysipelas and ulcers resulting in scars after resolution.<sup>7</sup>
- Macular RR with hypochromic or erythematous maculae, sometimes with local hypersensitivity. This presentation is common in patients with the borderline form after completing the specific treatment.<sup>8</sup>
- Cutaneous lesions similar to papulae and small disseminated plaques, mostly in MB patients.

**Extracutaneous manifestations and laboratory findings**

Certain aspects of the type I reaction in MB patients, although usually found in type II reactions, may present with systemic symptoms and significant laboratory findings. At our unit, 57% of 42 patients with type I reaction presented only cutaneous lesions, while 43% had systemic manifestations.<sup>9</sup> Unilateral or bilateral edema of the extremities or in unusual locations (such as the periorbitary region), mucosal edema (lips or penis), and generalized edema (anasarca-like) are reported.<sup>10</sup> Fever, malaise, adynamia, nasal obstruction, bone pain, lymphadenomegaly and arthralgia are present, specially in patients with the BL form.

In clinical practice, immunologic activity can be assessed in patients with RR during episodes of reverse reaction: high levels of neopterin,  $\beta$ 2-microglobulin, adenosine deaminase (ADA), tumor necrosis factor alpha (TNF- $\alpha$ ) and its receptors. Regression may be seen after corticosteroid treatment.<sup>11</sup>

**Histopathology**

RR may be characterized histologically by granulomas composed of many epithelioid and giant binucleated or multinucleated cells, rarely of the

**CHART 1:** Clinical differentiating aspects of RR in patients with MB and PB leprosy

	<b>RR-PB</b>	<b>RR-MB</b>
Plaques	Well defined	Ill defined
Neural involvement	Acute/Localized	Subacute or chronic
Disseminated/Systemic involvement	No	Yes
Edema of limbs	Unilateral, localized	Bilateral, diffuse

RR = reverse reaction, MB = multibacillary, PB = paucibacillary

Langhan's type. These granulomas are accompanied in most cases by epidermal thickening, moderate dermal edema, and a variable number of lymphocytes forming a lymphocytic halo around the granulomas. The dermal nervous bundles, almost always visible in biopsies, present few morphological findings in recent lesions, and are always surrounded and compressed by granulomas and edema. This histological finding is compatible with the hyperesthesia symptoms of RR lesions and the accompanying neuritis. The amount of bacilli varies according to the initial clinical form and duration of treatment. When present, they are granulous or fragmented, and plasmocytes are often seen in the perivascular inflammatory infiltrate. Variable extravasation of red blood cells is common.

## TYPE II REACTION

### Pathophysiology

Even though the type II reaction is usually described as an immunocomplex mediated reaction, some authors demonstrated a transient increase of cell-mediated immunity by showing increased serum TNF- $\alpha$  and interleukin-1 (IL-1) levels.<sup>12</sup> This type of reaction has been equated with erythema nodosum, although often presenting only the systemic symptoms without the classical cutaneous lesions. The cutaneous lesions of erythema nodosum are important signs of the type II reaction, but are not the only findings in this condition.<sup>13</sup> Occasionally cutaneous lesions present as erythema multiforme (EM) accompanied or not by neuritis.

### Erythema nodosum leprosum

It may be clinically characterized by the sudden appearance of dermal or subcutaneous erythematous inflammatory nodules, mobile on palpation, often painful, with local heat, that may progress to vesicles, bullae or ulcers.<sup>14</sup> Cutaneous lesions may assume different aspects other than typical nodules.<sup>15</sup> Occasionally indurated lesions (phlegmons), also known as panniculitis, appear in the posterior region of the upper and lower limbs. Nodules are bilateral and symmetric, usually appear on the face and extremities on apparently healthy skin, occasionally close to pre-existing lesions. The mucosa, semimucosa, perineum, inguocrural region, scalp and axilla are not affected. The nodules last from 8 to 10 days up to a few weeks.<sup>16</sup> Vieira<sup>17</sup> reported a case of ENL lasting over six months. Resulting hyperchromic areas after ENL regression are named contusifiform lesions.

### Erythema multiforme in leprosy (EM)

Patients may present erythematous purpuric macula and plaque-like lesions, which eventually pro-

gress to vesicles and bullae that may rupture, forming ulcers;<sup>18</sup> ulcers may coalesce and become polycyclic. The typical lesion is the herpes iris of Bateman, which is a blister that occupies the center of the lesion and is surrounded by concentric circular plaques.<sup>19</sup> Upon regression, there is fine scaling similar to a collarete on the surface of the lesion, which facilitates the differential diagnosis with other reactional states. In endemic countries the hypotheses of leprosy should always be raised when facing conditions of erythema multiforme of unknown origin which are refractory to conventional treatment; in such cases, bacilloscopy is mandatory.

If not carefully investigated, EM may be mistaken with RR, particularly in the BL form. EM occurs in approximately 8% of cases compared to the other reaction types.<sup>20</sup> Vieira et al. observed that EM type reactions are longstanding conditions, which require corticosteroid therapy associated with other medications such as pentoxiphylline and/or thalidomide for adequate control.<sup>17</sup> Concomitant EM and ENL lesions occurred in about 15% of multibacillary patients seen by the authors of this study. Other less frequent type II reaction states are the Lucio's phenomenon<sup>21</sup> and the auto-aggressive leprosy.<sup>22</sup>

### Histopathology

The ENL type lesion is characterized by dermal and mainly hypodermal vasculitis, involving capillaries, veins and arteries.<sup>23</sup> There is significant edema of endothelial cells and vascular walls in these vessels, a mononuclear inflammatory cell infiltration of vessel walls, duplication and thickening of the elastic layer, dilatation of the lumen, congestion and angiogenesis. Rarely, there may be occlusion of the lumen by eosinophilic material. There are also epidermal and dermal alterations in typical nodular lesions, such as epithelial hyperplasia, a major inflow of lymphocytes and polymorphonuclear leukocytes into the dermis, deep dermal collagen hyperplasia and interlobular septa in the hypodermis. Bacillary fragments or granules are always present in the type II reaction, varying in quantity according to the duration of the disease and the specific treatment.<sup>20</sup>

EM is characterized by intense edema of the superficial dermis, which may progress to form subepidermal bullae, frequently with edema of the deep epidermal layers, occasionally with necrosis of isolated cells. Alterations in the dermis and in blood vessels are similar to those in the EN type reaction, although more intense and located around superficial dermal vessels. The hypodermis may be completely intact or may show typical EN hypodermatitis, albeit less intense. As mentioned above, bacilli are always present and show a granulous or fragmented aspect.<sup>20</sup>

### Extracutaneous manifestations and laboratory findings

The systemic clinical picture of the type II reaction may be characterized by intermittent, usually moderate evening fever, at times reaching 39° or 40°C.<sup>24</sup> Weight loss is significant, requiring a differential diagnosis with HIV infection in some patients. Weight loss may be associated with increased serum TNF- $\alpha$ , leading to cachexia. Lymphadenomegaly may be present but, different from other diseases with this sign, in leprosy there is no lymph node fistulization. Gland involvement has been observed, particularly involving the parotid gland. Other findings include subacute *cor pulmonale* secondary to recurring pulmonary embolism and simultaneous lower limb thrombophlebitis with deep panniculitis, edema and recurring erythema nodosum.<sup>25</sup> An additional finding was a pericardial friction sound heard in a patient during a type II reactional state. Reactional states may present as acute or chronic polyarthritis.<sup>26-29</sup> Radiographies of the limbs in these patients reveal erosion and subluxation,<sup>26</sup> as well as phalangeal pseudocysts, collapse and cupping of joint surfaces.<sup>3</sup>

Systemic manifestations may precede the appearance of cutaneous lesions, causing difficulties in diagnosis.<sup>31</sup> In a study of 43 patients with MB leprosy in our outpatient clinic, who developed the type II reaction, 23% presented only typical EN cutaneous nodules, whereas 77% of patients had cutaneous lesions associated with systemic manifestations.

Extensive systemic involvement requires laboratory monitoring of patients with type II reaction. The complete blood count may reveal marked leukocytosis, around 30,000/mm<sup>3</sup>, at times resulting in a leukemoid reaction. Neutrophilia is also invariably present in leukocytosis; there may also be a shift to the left. These findings together are typical of a blood count in sepsis. At times there is an abrupt fall in the hematocrit.

Significant changes in the urinary sediment may also be seen, usually interpreted as a laboratory diagnosis of nephritis or urinary tract infection. Findings include proteinuria, hematuria and pyuria.<sup>32</sup> However, if urine is cultured, there is no growth of pathogenic germs. At our clinic, patients with these alterations were treated only with thalidomide at 300mg/day for seven days, notwithstanding the recommendation of other health professionals to introduce antibiotics. In these patients, results became normal after 36 to 48 hours of treatment.

### NEURITIS

Neuritis is the onset of spontaneous pain or pain upon compression of peripheral nerve trunks, with or without localized edema or affected neurolo-

gical function. Primary nerve damage (neuritis) leads to changes in sensitive, motor and autonomous function. These changes lead to secondary damage due to trauma, abnormal pressure and infection.<sup>33</sup> Neuritis, as with the other types of reaction, results from the production of a huge quantity of immunological mediators due to the transitory activation of the cell-mediated immune response. Nociceptive pain, triggered by tissue injury and activation of sensitive receptors at the site of injured tissue<sup>34</sup> is a common symptom in neuritis as the inflamed or edematous nerve is entrapped in an osteofibrous tunnel.<sup>35</sup> This type of pain is usually reversible and may be relieved by corticosteroids or non-steroidal anti-inflammatory drugs.<sup>36</sup>

Nerve function may also be affected in the absence of pain, detected in the sequential examination of the patient.<sup>37</sup> This type of insidious and painless involvement has been described as silent neuritis.<sup>38</sup> The neurophysiological assessment is useful to diagnose this asymptomatic form of neuritis.

For classification purposes, isolated neuritis is the reaction that presents with nerve symptoms or signs with no cutaneous manifestations of RR or EN during follow-up (both during and after treatment). Pimentel,<sup>39</sup> assessed 103 patients with MB leprosy to study the role of neuritis in inducing and worsening physical disability, and observed that clear episodes of neuritis were usually associated with EN states (55.3%), compared with the incidence of neuritis in RR patients (33.3%), although this difference was not statistically significant.

Saunderson et al.<sup>40</sup> classified episodes of neuritis according to the clinical progression as follows: a) acute neuropathy - nerve thickening and/or new involvement of nerve function lasting at least six months associated or not with reaction symptoms (RR or EN); b) silent neuropathy - new involvement of nerve function accompanied or not by reaction symptoms (RR or EN) or nerve thickening; c) recurring neuropathy - a subsequent episode of acute neuropathy lasting at least three months after interrupting corticosteroid therapy during which no sign or symptom of acute neuropathy was observed; d) chronic neuropathy - signs of active neuropathy (nerve pain or thickening or new involvement of nerve function) within three months after interrupting corticosteroid therapy.

The pain in neuritis should be differentiated from neuropathic pain, which is defined as pain resulting from a disease of or damage to the central or peripheral nervous system, usually indicating permanent nerve abnormalities.<sup>36</sup> Neuropathic pain syndromes are conditions with common clinical phenomena such as spontaneous burning pain, different types of

allodynia or pain as a shock-like sensation. This type of pain should be recognized in leprosy patients because neuropathic pain does not respond to steroidal or non-steroidal anti-inflammatory drugs. Tricyclic antidepressants, anticonvulsive agents, opioids or topical lidocaine are effective in the treatment of this type of pain.

#### OTHER TYPES OF REACTION

**Mixed reaction:** patients that simultaneously or not present type I and II reaction states, regardless of follow-up time, are included in this classification. It occurs mostly in the BL form. This presentation has been a research topic at the *Instituto Oswaldo Cruz*. Its frequency is roughly 8.8% compared to other reaction states in multibacillary patients.<sup>41,42</sup>

**Atypical reaction:** this is an unusual presentation that does not fulfill reaction criteria described in literature, but which responds favorably to anti-reactional medication. Among typical forms we see isolated significant involvement of the parotid gland, arthritis, lymphadenomegaly, important weight loss, acute respiratory distress, lumbar pain, orchitis, anasarca-like edema, and cutaneous involvement that may present non-classical lesion which complicate the diagnosis.

#### Prodromes

These are signs and symptoms preceding the appearance of classical reactional cutaneous features, such as generalized cutaneous pruritus that may present as hyperesthesia and which may precede the type I cutaneous reaction by weeks. Palmar and plantar and/or pinna hyperesthesia and unilateral edema of extremities may also occur. The type II reaction may be preceded by lymphadenomegaly, malaise, generally bilateral edema of the extremities, fever and nasal obstruction.

#### OPERATIONAL ASPECTS

##### Onset of the reactional state

RR episodes occur mainly during the first six months of polychemotherapy (PCT) in BT and BB patients; longer intervals are seen in BL patients.<sup>5</sup> However, a reactional state may arise as an initial presentation symptom, or more commonly, following treatment.<sup>43,44</sup> This is becoming clearer in the type II reaction, showing that its distribution occurs in all stages of PCT and after treatment.<sup>45,46</sup> Nery<sup>9</sup> observed that 57% of patients with EN had a reactional state during the first year, and that 20% of patients already were in a reactional state upon diagnosis of the disease. A further observation was that isolated neuritis occurs mostly during the first 12 months of treatment.

For the sake of uniformity, the PCT dose at the time the patient has a reaction is annotated. Reaction episodes which occur after treatment has been concluded are reported on a monthly basis, including the data of occurrence.

#### Number of episodes

In general, a patient that has no symptoms or signs of a reaction while taking low-dose anti-reactional medication, who presents cutaneous, neural or systemic lesions, is considered as having a single reaction state. A type I, type II or neuritis reaction state is considered as new when typical signs and symptoms reappear three months after cessation of treatment of a given reaction state.<sup>47</sup> Patients are only discharged from treatment of reactions when there are no further dermatological, neurological and/or systemic signs and symptoms of this condition and when there is no longer any anti-reactional treatment.

#### Severity and complications

Reactional states may be classified as major (M) when there is involvement of the skin and other organs or when symptoms such as fever, arthralgia, myalgia, weight loss, epididymo-orchitis, iridocyclitis, neuritis, and other systemic findings are present, and minor (m) when patients present only cutaneous lesions.

Similar to other chronic inflammatory diseases, during a reaction state there is deregulation of the immune and inflammatory responses, leading to bone destruction. There is periarticular<sup>48</sup> or more generalized<sup>49</sup> demineralization in the limbs. Bone involvement such as periostitis, particularly in the tibia, was reported, and presents as pain upon local percussion.<sup>50</sup> Some authors suggested that osteoporosis occurring during reaction states is due to an inflammatory or neurovascular process.<sup>51</sup> Endocrine factors, such as hypogonadism<sup>52</sup> and prolonged use of corticosteroids, were also suggested as causes of osteoporosis in leprosy.<sup>53</sup>

Most reactional states can be monitored in an outpatient setting, although a few patients may require hospital treatment. Hospitalization is indicated when there are extensive ulcers, severe systemic manifestations, need for further clinical and laboratory investigation, and need for pulse therapy with endovenous methylprednisolone.

#### TREATMENT

The treatment of reactional states in leprosy follows protocols established by the Brazilian Ministry of Health.<sup>54</sup> Briefly, the type I reaction is treated with corticosteroids in a dose of 1mg/kg/day until regression of the clinical picture, followed by gradual

dose reduction. The type II reaction is treated with 100 to 300mg/day of thalidomide until full regression of the condition; thalidomide is not given to women at child-bearing age due to its teratogenic effects. The alternative in these cases and when there is EN with neuritis, edema of the hands and feet, iritis, iridocyclitis or orchitis, or whenever thalidomide is not indicated,<sup>55</sup> is to use corticosteroids.

The treatment of chronic EN cases or those that do not respond satisfactorily to corticosteroids, or when this medication is a high risk drug for specific patients, is to use 300mg/day of clofazimine for not more than 90 days, in association with corticosteroid therapy.

Pentoxyphilline has been used successfully in type II reactions with significant improvement over a two-week period; nodular lesions also regress if the drug is used for more than two weeks. The advantage of this medication is that it may be used by women at child-bearing age, since there are no teratogenic

side effects. The dose of pentoxyphilline is 400mg every eight hours, associated with prednisone. With clinical improvement, usually after 30 days, the dose of prednisone is gradually reduced, and pentoxyphilline is maintained for another two to three months. Prednisone in association with the two drugs mentioned above is used in a dose of 0.5mg/kg/day.<sup>56</sup> At the *Instituto Oswaldo Cruz*, pentoxyphilline has been used as a single drug for the treatment of type II reactions with promising results.<sup>57</sup>

Azathioprine has been used in an attempt to avoid corticosteroid use or to increase its immunosuppressive effect; the dose is 150mg/day (50mg three times a day) *per oris* for not more than six months. The patient should be monitored monthly and a complete blood count and blood biochemistry tests should be done every two months. If side effects arise, drug treatment is interrupted. Some patients have remained with no cutaneous or neural lesions with azathioprine and low-dose corticosteroid therapy.<sup>58</sup>

**CHART 2:** Differences between type I and II reactions

Reaction	Type I	Type II
Most frequent onset	In the first 6 to 12 months of PCT	After 12 months of PCT
Clinical forms	BT, BB, BL and LL	BL and LL
Usual presentation	Monomorphic condition: erythematous plaques, of many sizes and shapes, scaling of the whole lesion	Polymorphic condition: nodules, plaques, papulae, vesicles, bullae and ulcers, fine scaling of part of the lesion
Localization	Trunk and limbs – localized lesions	Face and limbs – disseminated lesions
Prodromes	Cutaneous hyperesthesia on palmar and plantar regions and pinnae, generally unilateral edema	Fever, arthralgia, myalgia, malaise, generally bilateral edema, lymphadenomegaly and nasal obstruction
Atypical clinical forms	Macular RR, pseudonodules, anasarca-like edema	Inflammatory parotiditis, orchitis, lymphadenomegaly, significant weight loss
Systemic alterations	Only in MB patients	Yes
Mechanism involved	Reactivation of cell-mediated immune response	Reactivation of the humoral and cell-mediated immune response, increased TNF- $\alpha$ production
Histopathology	Epithelioid granuloma	Mononuclear and polymorphonuclear inflammatory cell infiltrate, vasculitis
Laboratory findings	Only in MB patients	Yes
Treatment	Prednisone: 1mg/kg/day	Thalidomide: 100-300mg/day Women in procreating age: Prednisone: 1mg/kg/day Pentoxyphilline: 1,200mg/day

Endovenous methylprednisolone (EVMP) or pulse therapy has been used to facilitate withdrawal of oral corticosteroids used to control reactional states; the aim is to reduce side effects and the period of morbidity. Indications for use of EVMP are reversal reaction, erythema nodosum, widespread and difficult to control erythema multiforme, acute or chronic neuritis cases that have already undergone prolonged oral corticosteroid therapy. The dose is 1g of EVMP as a single daily dose during three days in the first week, followed by 1g as a single weekly dose during four consecutive weeks, and followed by 1g as a single monthly dose during four consecutive months. Between pulse therapy, 0.5mg/kg/day of prednisone is used. The dose of prednisone is gradually reduced

following the same criteria described above for its withdrawal.<sup>59</sup>

#### FINAL COMMENTS

Differences in types of reactional states and their presentation are paramount, given the importance of the correct management of these states to avoid complications and sequelae (Chart 2). Care should also be taken with the specific treatment to avoid iatrogenesis. The association of anti-reactional drugs with different mechanisms of action may be clinically useful in an attempt to increase the anti-inflammatory effect with lower doses and to decrease the treatment time for reactional states. □

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