American Journal of Neurology Research

Research Article

Contribution of Skin Biopsy in the Diagnosis of Restless Legs Syndrome

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Received: May 06, 2024; **Accepted:** June 18, 2024; **Published:** June 24, 2024

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Citation: Emmanuel Yangatimbi, Duval Lewis Grenaba, Caprice Vivien Ndouellet, Josué Pierre Kinima, Larissa Kpengougna, et al. Contribution of Skin Biopsy in the Diagnosis of Restless Legs Syndrome. American J Neurol Res. 2024; 3(1):1-4.

ABSTRACT

Introduction: The diagnosis of restless legs syndrome (RLS) is an exclusively clinical diagnosis which is based on questioning the patient. Furthermore, several pathologies can mimic the symptoms of RLS. It should also be emphasized that small fiber neuropathies (SNF) escape electroneuromyography (ENMG) since this examination essentially studies large diameter myelinated fibers. The objective of this study is to assess the contribution of skin biopsy on the one hand in the differential diagnosis of RLS when an associated pathology may be responsible for NPF and on the other hand in the diagnosis of RLS with tone very painful.

Patients and Methods: We carried out a prospective study covering the medical files of 2 patients followed in consultation at the Limoge University Hospital for RLS, one of whom had a systemic disease and the other had RLS evolving since then through attacks. unbearably painful. Each patient underwent a clinical evaluation based on the diagnostic criteria for RLS, an ENMG and a skin biopsy.

Results: For each patient, the diagnosis of RLS was confirmed by the presence of four diagnostic criteria. Patient 1 had an IRLS score of 30/40, a normal ENMG and a normal skin biopsy with normal FNIE density. Patient 2 had RLS with a very painful tone, a normal ENMG and a skin biopsy showing rarefaction of FNIE proximally and distally, and concomitant rarefaction of subepidermal fibers.

Conclusion: This study, considered preliminary with a limited sample, does not allow us to achieve the objective. A longitudinal study with a satisfactory sample could allow us to elucidate the question.

Keywords

Restless legs syndrome, Diagnostics, Skin biopsy, Limoges University Hospital.

Introduction

Restless leg syndrome (RLS) is a common neurological pathology, characterized by an unpleasant sensation and an urgent need to move the lower limbs, occurring as soon as the patient is at rest immobile, in the evening and at night, improved by movement. It can be associated with repetitive motor agitation, either voluntary or involuntary, with a type of abrupt and spontaneous movement of the legs during wakefulness and sleep, which is called Periodic Leg Movement (PMJ) [1-4]. The prevalence of RLS in adults in the general population of Western Europe and North America is 7 to 11%, with twice as many women affected as men and an increase in prevalence in both sexes with the age [2,5,6]. The pathophysiology

of RLS is complex and clearly involves genetic and environmental factors. The diagnosis of RLS is an exclusively clinical diagnosis, which is based on questioning the patient. Several pathologies can mimic the symptoms of RLS. If the diagnostic criteria for RLS [1] are correctly applied by the clinician and if the latter takes into account certain differential diagnoses, the positive diagnosis of RLS is easy. The majority of cases of RLS are primary or idiopathic. They are then either familial with a strong hereditary component, or sporadic. But the syndrome can be secondary or amplified by iron deficiency, pregnancy or end-stage renal failure.

Small fiber neuropathies (NPF): These are pure sensory neuropathies whose predominant clinical expression is neuropathic pain, due to the exclusive involvement of small myelinated fibers and unmyelinated fibers of type A delta and C, conveying the thermal and algic for superficial sensitivity. Damage to vegetative fibers may be associated. The mainly distal distribution of these neuropathies most often leads to a picture of [burning feet] [7,8], although much more diffuse damage has been reported. The clinical examination of patients suffering from NPF is often poor, consisting of isolated thermo-algesic hypoesthesia associated with normal osteotendinous reflexes and of course muscular strength [9]. The presence of allodynia seems to be frequently found during questioning or clinical examination. The causes of NPF are very diverse but in a recent series. A cause was only found in 25% of cases after a two-year follow-up [10]. It also seems clear that certain cases. As for example in diabetes, NPF evolves into peripheral neuropathies also affecting large myelinated fibers. In addition to the clinical examination, some additional examinations can contribute to the positive diagnosis of NPF: skin biopsy, quantified sensory testing (QST), nociceptive or laser evoked potentials. Concerning the study of sensitive nerve conductions, it must be emphasized that only large caliber fibers (Beta) can be explored and in no case weakly myelinated (A delta) or unmyelinated (C) small caliber fibers. The authors report two (2) cases of RLS, the objective of which is to assess the contribution of skin biopsy in the differential diagnosis of RLS when an associated pathology may be responsible for NPF and in the diagnosis of RLS with very painful tone.

Materials and Method

This is a prospective study involving two patients followed in consultation at the Limoges University Hospital for restless legs syndrome.

Case 1: Ms. Christel M., aged 39, was referred in 2022 for evening-night burns of the lower limbs. These burns are clearly improved by walking. The criteria for RLS are met. The patient also suffers from systemic lupus erythematosus and heart disease. The treatment of Ropinirole® relieves the patient. However, the profit fluctuates. A certain balance is found after adding Clonazepam®.

Case 2: Mr. Roland L., aged 66, was referred in 2022 for severe pain in the lower limbs, with paroxysmal resurgence, and improvement with walking. The criteria for RLS are met. The patient is much improved by Pramipexole®, although he has persistent paroxysmal gastric crises. The patient is also followed by hematology for kappa type AL amyloidosis with isolated gastric and duodenal localization, responsible for a hemorrhagic ulcer. The myelogram is normal.

Clinical

Diagnostic criteria: The diagnosis of RLS is an exclusively clinical diagnosis which is based on questioning the patient. Four criteria are essential to the diagnosis and must be present to make the diagnosis:

- An urgent need to move the limbs (most often the legs) usually accompanied or caused by unpleasant, painful sensations in the leg. The supervising limbs may also be affected in severe and sometimes need to move is present without unpleasant sensations.
- Symptoms begin or worsen during periods of rest or inactivity, while sitting or lying down.
- They are partially or totally relieved by movement (walking, stretching) at least as long as the movement lasts.
- They worsen or only occur in the evening or at night

IRLS score

Once the diagnosis of RLS has been made, it is necessary to assess the severity of the syndrome. There are two validated clinical severity scales for RLS. The John Hopkins Group Scale [11], and an international scale, IRLSSG Rating Scale [12]. This last scale is a self-questionnaire of 10 questions which allows patients to be classified into 4 groups according to whether the syndrome is of mild severity (score 0 to 10), medium (11 to 20), severe (21 to 30) or very severe. severe (31 to 40). This scale is useful for monitoring patients and judging the therapeutic effect (International Restless Leg Syndrome Severity Scale. IRLSSG Rating Scale).

Electroneuromyography (ENMG)

The ENMG examination is designed as an extension of the clinical examination. This examination makes it possible to define the site of the lesion (truncular, radicular or the body of the motor or sensory neuron), to determine the mechanism (axonal or demyelinating), to direct towards the etiological diagnosis and to establish an evolutionary prognosis. Concerning the study of sensory nerve conductions, it must be emphasized that only large caliber fibers (A-beta) can be explored and in no case weakly myelinated (A-delta) or unmyelinated (C) small caliber fibers. Specific neurophysiological methods are applicable to the study of small fibers.

Skin Biopsy

Over the past fifteen years, many internationals have reported the value of skin biopsy in the diagnosis of NPF. The reduction in the density of intra-epidermal nerve fibers (FNIE) currently constitutes a robust confirmation criterion for NPF in selected bleeding subjects [1]. According to studies, skin biopsy offers high sensitivity and specialty for the diagnosis of NPF [10-12]. However, the loss of fibers reflects an already advanced process and could be preceded by a phase of axonal disturbances, without

total destruction of intra-epidermal nerve fibers (INEF). Thus, certain morphological anomalies, such as axonal dilations, these anomalies precede the disappearance of the fibers [13]. In addition to quantifying FNIE, analysis of dermal nervous tissue can provide very useful additional information. Thus, the quantification of Meissner corpuscles (sampled from glabrous skin, generally on the lateral side of the index finger) provides information on the loss of myelinated fibers [14]. The innervation of sweat glands has also been the subject of quantification work, making it possible to non-invasively approach fiber loss in the autonomic nervous system [15]. Skin biopsy has its place in the positive diagnosis of NPF by showing a rarefaction of epidermal fibers. However, it's still relatively limited availability on French territory, and the absence of large normative data from a French population are an obstacle to their routine use for the diagnostic confirmation of NPF. Above all, we must keep in mind that skin biopsy has not yet shown a certain benefit in the etiological diagnosis of NPF, even if recent work allows us to envisage new developments in the technique [16-18].

Results

Patient 1: Mr. Christel, born 03/02/1969 married with two children.
• IRLS score of 30/40 confirming severe RLS.
• ENMG: sensory and motor stimulation is normal. No evidence for underlying neuropathy.
• Skin biopsy carried out on 06/26/2022, No. 992 in the neurology department of Limoges University Hospital.
Indication: Burning of the lower limbs. Sampling area: thigh and leg.
Technique: Indirect immunofluorescence (AC anti PGA 9.5: Ultraclone, UK)
Results: Density of intra-epidermal nerve fibers (FNIE)*: Proximal +++ and distal +++
NB:
• *The result is expressed in number of FINIES per unit of length (mm)
• **the density of subepidermal nerve fibers is expressed semi-quantitatively as follows: +++ = normal density, ++= reduction in density, += severe reduction in density and 0= absence of fiber. However, the skin biopsy data must be compared to the clinical context.

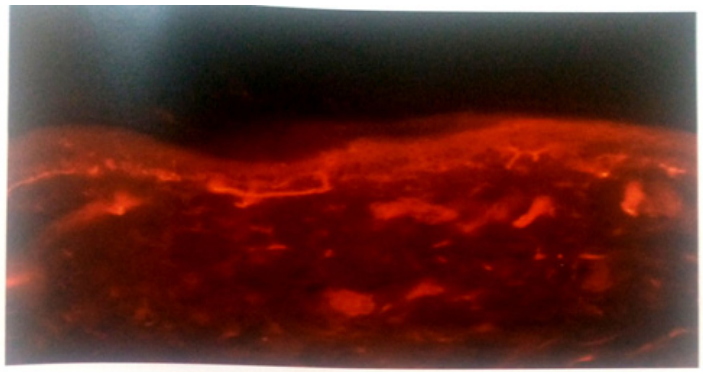

Photo 1: Skin biopsy of Mr. Christel, distal portion. *

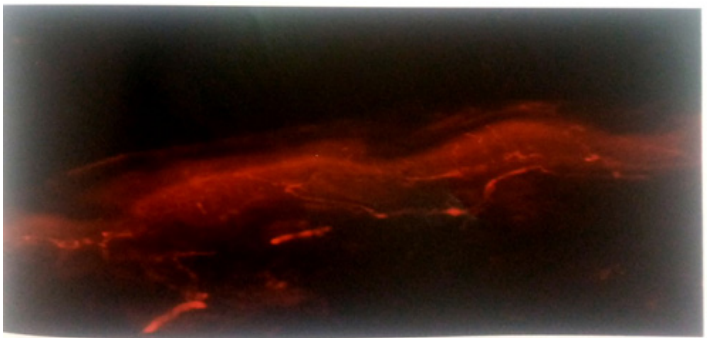

Photo 2: Skin biopsy of Mr. Christel, proximal. * (* source: Professor Laurent Magy)
Conclusion of the skin biopsy: Normal FNIE density.

Patient 2: L. Roland born 07/12/1942.
• IRLS score in favor of RLS
• **ENMG:** at least 4 ENMGs were performed with normal sensory and motor stimulation. No evidence for neuropathy, however, sensory amplitudes at the lower limit of normal (results in appendices)
• Skin biopsy carried out on 10/28/2022 No. 781 in the neurology department of Limoges University Hospital.
Indication: Pain in a patient with localized amyloidosis. Same sampling area and technique.

Results

Density of intra-epidermal nerve fibers (FNIE)*: Proximal 5.7/mm and distal 3.6/mm.
Density of subepidermal nerve fibers:** Proximal: + and distal: +
Conclusion of the skin biopsy: Rarefaction of FNIE proximally and distally. Concomitant rarefaction of subepidermal fibers.

Photo 3: Skin biopsy of L. Roland, distal portion. *

Discussion

Clinical Case 1: This patient has typical RLS associated with systemic lupus erythematosus and celiac disease. Peripheral neuropathies are another potential cause of RLS. However, this association remains controversial, especially since it is difficult to establish a causal relationship between peripheral nerve injury and RLS symptoms; It is impossible to routinely explore unmyelinated fibers and difficult to rule out peripheral nerve damage through

a normal clinical examination. Furthermore, the frequency of the association between RLS and neuropathy varies greatly depending on whether symptoms of RLS are sought in patients with neuropathy or whether signs of neuropathy are sought in patients affected by RLS. Whatever the configuration, the prevalence figures do not agree from one study to another. The association of RLS and peripheral neuropathy, especially axonal, is classic [19] and it is legitimate to look for neuropathy in any patient with RLS and to look for RLS in any patient with a neuropathy, particularly hereditary [20]. However, the frequency of this association varies from one study to another. Studies investigating neuropathy in patients with RLS have also produced conflicting results with prevalence figures ranging from 2.7 to 36%. In 8 patients with an idiopathic form of RLS and with a normal standard electromyographic examination, nerve biopsy found discreet signs of axonal damage [21]. BrannaganTH et al. [22] in a study carried out in North America had shown patients with celiac disease can have NPF, demonstrated by biopsy results. However, the mechanisms of these NPFs remain uncertain. In this patient with celiac disease and systemic lupus, the imperfect control of symptoms could raise fears of the presence of small fiber neuropathy. After a negative skin biopsy, the explanation was ultimately hyposideremia secondary to malabsorption. Iron treatment improved the pain.

Clinical Case 2: This is a patient with atypical RLS and localized amyloidosis.

Some authors have isolated a form of atypical RLS, frequent, without periodic sleep movements, not responding to dopaminergic substances, often severe and associated with depression occurring in young subjects and responding to antidepressants. It could be an atypical form of RLS with a different phenotype and perhaps a genotype or a different disease from RLS [23]. It should also be emphasized that small fiber neuropathies escape ENMG since this examination essentially studies large diameter myelinated fibers. The diagnosis of small fiber neuropathies is difficult because the neurological examination may be normal and routine examinations to make the diagnosis are lacking. The use of more sophisticated electrophysiological methods such as nociceptive evoked potentials currently makes it possible to have objective criteria for the diagnosis of these neuropathies [24]. Small fiber neuropathy was also found on skin biopsies in 36.4% of patients in whom the standard electromyographic examination remained normal [25]. In this series, the authors conclude that there are two forms of RLS: the first; painful and dysesthesia associated with damage to small nerve fibers, appears in elderly subjects without a family history of RLS, and the second non-painful form without damage to small fibers, appears in young subjects with a family history of RLS. In this specific case where the ENMG is normal requiring specific explorations: laser evoked potentials and skin biopsy; the etiologies are diverse, acquired or hereditary [26]. Acquired causes include diabetic neuropathies, amyloids, leprosy, HIV infection and certain systemic diseases (such as sarcoidosis). Among the hereditary causes, Tangier disease, Fabry disease and hereditary amyloidosis should be noted. Concerning our patient, the occurrence of RLS in very painful attacks, in a context of digestive amyloidosis and having sural amplitudes bordering on the ENMG, the possibility of an amyloid neuropathy led to a skin biopsy being performed in a first time. The rarefaction of FNIE will lead us to propose a sural nerve biopsy.

Conclusion

RLS is a chronic neurological syndrome characterized by the presence of a painful sensory component and a motor component with well-defined diagnostic criteria. In the event of a clinical abnormality, additional investigations are essential in order to determine any associated pathologies. RLS can be associated with different pathologies including polyneuropathies, which represent, among the secondary forms, the most frequently encountered etiologies. This preliminary study aimed to assess the benefit of skin biopsy in particularly painful RLS, or accompanied by a condition that can lead to small fiber neuropathy. A longitudinal study with a satisfactory sample could allow us to fully elucidate the question.

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