Topical phenytoin in a case of severe fibromyalgia: ex juvantibus proof for fibromyalgia as a localized non-length dependent small fiber neuropathy

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Abstract
We present a case of a 52-year old woman suffering from severe fibromyalgia, unable to manage even the lightest of housework, she gradually became crippled and her life became a ‘couch potato’ in patient’s own words. Treatment with topical phenytoin (5% titrated up to 15%) transformed her life, pain nearly vanished, and she became active, looking for a job, doing housework and she can walk rapidly. One explanation of this phenomenon could be that a number of patients suffering from fibromyalgia and having tender points suffer from localized length non-dependent small fiber neuropathy, and this pathology can be found in the skin above the tender points.

Keywords: Neuropathic, treatment, formulation, pain, SFN.

Case description
The patient we present to you, a 52-year old woman seen first in November 2013 suffering from chronic fibromyalgic pain during many years, used to take 4 or 5 minutes just to walk down the corridor to the physician’s office, her clothes were always loose, she never wore a bra due to the severe pain of putting it on, her husband helped with most of the housework, and even light housework for her was too much. Many different analgesics where tried, but none helped. After starting treatment with topical phenytoin, she now is a new woman, looking for a job, doing housework, walks rapidly, and the impression is that her ‘new body and life’ results in her exploding with joy.

The patient was first seen in November 2013 at the age of 52 upon referral regarding a narrow band of pain across her chest and back at the D4-5 level. The pain and sensitivity had gradually increased after a very minor back bump in the course of her housework. This has been extremely well investigated with a number of MRIs, neurological consultations but with no resolution. The pain was of such severity that she was unable to work, wear tight clothing particularly a bra. From working full-time at a heavy job, she was unable to manage even the lightest of housework and gradually became crippled. Following the above-mentioned pain, she developed symptoms suggestive of Fibromyalgia which gradually escalated in intensity and became intrinsic to her health and lifestyle.

Examination revealed a pleasant woman who even needed help getting out of the chair as the pain in her back was so intrusive score 8-9 on an 11-point NRS. Her pain tolerance using a Fischer Probe (figure 1) was reduced in her arms and to a lesser extent in her legs. Even applying the probe without pressure on the piston produced considerable pain. The area of pain corresponded to an area of hyperesthesia running from D4-5 like a band around her body. The skin over the area showed very significant hyperesthesia, with cotton wool producing significant pain. Tender point count was 18/18 on a A.R.C. scale. Her mood was quiet and debilitated. The pain inhibited her sexual life and greatly her sense of well-being. In the past she had taken a wide range of analgesics, neuroleptics, anti-depressants, and pure analgesics to no effect.

Her medical treatment at that time consisted of amitriptyline 50 mg at night, gabapentin 600 mg five times per day, which provided minimal help. Progress – over the years, a full spectrum of supportive vitamin therapies was tried, oxycodone, trigger point therapy. The use of a topical mixtures of NSAIDS, with lidocaine were somewhat helpful but transient and over time seemed to lose its effectiveness. During this time, her health stabilized but she was still quite incapacitated. The use of cannabinoids provided no significant change and was abandoned. A further neurological investigation and consultation provided no cause for the band of chest pain. She was grateful for the attempt to help the pain, but we were making no significant improvement. Wishing to leave no stone unturned, she was even started on micro-dose lithium up to 1mg, again without any significant change.

Figure 1. A Fischer Probe is a pressure algometer, increasing pressure on the skin at a constant rate until the pain threshold is reached and the current pressure is measured.

In January 2018, we started treatment with topical phenytoin, 5%, titrating up to 15%. Her improvement was in a straight line and gradually over the ensuing few months, the pain decreased significantly. She was able to walk at speed, carry out housework, and wear clothes that touched her skin with total relief of pain.
Over the next few months, the pain over her tender points became less and less as measured by a Fischer Probe (a tonometer or pressure gauge) reading 5-6 which is a normal value in these areas demonstrating a return to normality. Her sensitivity was so great that the slightest pressure from the rubber piston of the probe initially would produce pain and after treatment there was very little sensitivity to the probe pressure.

With her positive response, the physician and patient both agreed that the high dose of gabapentin would be slowly reduced, and this is now at 550 mg/daily rather than the previous 3000 mg/daily. With the gradual reduction of gabapentin, she was started on phenytoin in a dose 50 mg once per day. The most impressive improvement of her health has been in the control of her back pain and the tender point pain. The reduction of high doses of gabapentin and the addition of phenytoin subsequently also has helped and added quality of life.

In order to add some extra perspective to this case we briefly present a second patient: The second case was a woman, 42 years-old with many medical conditions including a spectrum of autoimmune disorders including Multiple Sclerosis and Rheumatoid. After a number of years, she developed fibromyalgia increasing in intensity with the onset of her other disorders. The pain increased in intensity and spread. We failed to produce controllable levels even with the addition of narcotics in a hospital setting. She was started on topical phenytoin 5% and then 10% which produced a remarkable contraction of the painful area around the tender points which occurred within a few days. These decreased in sensitivity as measured by a Fischer Probe. She was subsequently started on oral phenytoin, 20 mg b.i.d.

Discussion

The treating physician, ALR, based on 50 years of medical practice had never seen such a transformation from couch potato (patient’s own words) to an active woman looking for a job. Topical phenytoin has been selected as a broad acting sodium channel blocker for the development of a compounded formulation in 2015. [1] It has been tested in open and single blind test paradigms in a number of peripheral neuropathic pain states. [2-4] Its mechanism of action is intradernally, plasma levels could not be measured 2 hours after application. [5] What could be the reason of this positive reaction of fibromyalgic pain after treatment with phenytoin cream? Ex juvantibus refers to the process of identifying the cause (in this case the pathogenesis) of a disease based on observed response of a patient to a specific treatment. In our case the fact that this patient responded so clearly after the treatment with topical phenytoin suggests that the pathogenesis, at least in this case, also resides in the skin, as we have demonstrated the absence of systemic effects.

Fibromyalgia and trigger points perhaps to a lesser degree have been one of the failures of medical science. Fibromyalgia first entered the literature over 200 years ago and has been certainly aggressively investigated over the past 100 years to little avail. It is a worldwide dysfunction although the tender points have different calculations, it is the same illness. Like many disorders in medicine, it has gone through various cycles of etiology, pathogenesis, treatment and being unable to be reproduced in the lab, diagnosed accurately or treated, it has sometimes been labelled psychosomatic. To this day, we still do not have a definitive and effective treatment. Trigger points were in a similar dilemma, the work of Janet Travell and her famous patient, President Kennedy, put this subject on the map. There is little doubt that trigger point therapy is effective in many cases with the injection of local anesthetic, why they happen in recurrence has been a puzzle. Having treated trigger points for the last 30 years one is impressed by their response to local anesthetics, often repeated to the next cycle of trigger points appear. The question of why has not been defined. Like most things that are not well defined or understood, various treatments have been tried extensively on Fibromyalgia to little effect. The importance of sleep has led to a considerable number of trials using a range of sedatives to antidepressants.

Whether disrupted sleep is cause or effect is still somewhat uncertain although early studies of waking healthy students every hour developed a pattern similar to Fibromyalgia.

Over the years, treating trigger points in patients with a fair degree of success has been very satisfying. Fibromyalgia on the other hand has been depressing to manage, a percentage of cases seem to spin out of control with pain, spasms, insomnia, depression, and a sense of hopelessness in some cases as doctors try one favorite drug after another. Trigger point therapy is only partially effective and temporary. Why the pattern which is very definite is another failure of medical science.

From numerous clinical observations and papers, it is obviously a cycle of dysfunction between the periphery and the central nervous control. The question is why? How can this cycle be broken?

Our work on the treatment of diabetic and other causes of peripheral neuropathies using topical 5-10% phenytoin cream helped us to define the pathogenesis of many peripheral neuropathic pain states to reside in the skin. Together with Professor Notermans, from the Utrecht Academic Medical Centre in the Netherlands, we discussed the pathogenesis of a number of small fiber neuropathic pain states, and linked this pathogenesis to the pain reduction in these patients after applying a broad acting sodium channel blocker such as phenytoin. [6] Recently it was found that more than half of the patients presenting with neuropathic pain and who met diagnostic criteria for fibromyalgia had small fiber neuropathy, detected by skin biopsy testing. [7]

Our fibromyalgia patient was so helped by topical phenytoin, that she also commented on her husband using it for arthritis and her mother-in-law for cancer pain. Topical phenytoin has been reported to be of use in the treatment of various peripheral neuropathic pain states. [5] This however is the first report where topical phenytoin seems to reduce pain in fibromyalgia, and the reported effects might be related to the existence of small fiber neuropathy in this fibromyalgia patient. A significant number of fibromyalgia patients with positive trigger points might actually be suffering from a wide spread non-length dependent small fiber neuropathy. This is the first time this hypothesis has been launched as far as we know.

Conflicts of interest

JMKH is holder of two patents: topical phenytoin for use in the treatment of peripheral neuropathic pain and topical pharmaceutical composition containing phenytoin and a (-)-asalic for the treatment of chronic pain.

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References