Old Obstacles but New Hopes: Trying to Understand the Fibromyalgia Construct

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Fibromyalgia is a chronic debilitating disorder characterized by widespread pain, allodynia and hyperalgesia on one hand, with fatigue, unrefreshing sleep accompanied by mood and cognitive disturbances on the other. It affects 5% of the population worldwide with a clear female preponderance [1]. More than two decades ago fibromyalgia was acknowledged and defined by classification criteria that underlined the somatic aspects of the disorder. This set of criteria was adopted by the American College of Rheumatology (ACR) [2]. Within the last 4 years the diagnosis of fibromyalgia has progressed, emphasizing the importance of the symptoms beyond pain. The new suggested criteria take into consideration additional symptoms mentioned above [3].

Despite significant achievements in the field of fibromyalgia research linking it to various neurophysiological mechanisms, many physicians still regard fibromyalgia as a controversial entity since there is no objective test to confirm the diagnosis [4]. The diagnosis is further complicated by the stigmatization of this disorder among treatment providers, the health insurance industry, and the general population. The immense financial and emotional burden of this syndrome reflects the complexity of the disease, its comorbidities, and the difficulties in its diagnosis [1].

The financial burden of fibromyalgia is substantial, with reported health care costs (for 12 months) ranging from $2274 to $9573 in the United States and up to $2298 in Canada, not including indirect costs such as disability claims and loss of work days [5]. The health care system is utilized at significantly higher rates by fibromyalgia patients due to more frequent visits to the physician, laboratory and imaging tests and visits to the emergency department. In addition, these patients are more likely, as mentioned, to suffer from comorbidities and are more prone to receive pain-related medications [1,3,6,7].

TREATMENT

Treatment of fibromyalgia is a complex issue, encompassing a wide diversity of therapies – both pharmacological and non-pharmacological [6]. The most substantiated pharmacological treatments, with an A1 level of evidence, are norepinephrine serotonin reuptake inhibitors (milnacipran, duloxetine), gabapentinoids (pregabalin, gabapentin), tricyclic antidepressants (amitryptiline), and Y-amino butyrate. To date, no specific medication has been proven significantly more efficient than another, but most medications show an amelioration of 30–50% in pain in up to half the patients [1,6]. Many non-pharmacological therapies have been studied such as exercise, education, and cognitive behavioral therapy, the latter being the most investigated and the most substantiated [1,6]. In addition, many alternative and complementary therapies are offered, although there is a paucity of good evidence due to different problems in study design. Most guidelines emphasize the importance of education on the nature of the disease. Empowerment of an active patient stance towards the disease and its implication is seminal in order to achieve therapeutic success; such an intervention should include physical activity and cognitive behavioral therapy as crucial adjuncts to pharmacological therapies [1,6,8].

ADHERENCE TO TREATMENT

There is little research on adherence in fibromyalgia. In general it has been shown that adherence is higher in acute pain conditions compared to chronic conditions, and that improving adherence leads to reduced health care costs and improved patient quality of life [9,10]. Various barriers to adherence have been studied, including cognitive barriers such as fears regarding analgesic use (fear of addiction, etc.); concern of appearing weak to family, physicians and others; and a belief that pain is an inevitable part of the disease [10]. Other obstacles to improved compliance are psychological factors, patient-
physician discordance, not being under a rheumatologist’s care, comorbidities, and others. There is sparse literature on adherence specifically in fibromyalgia, and even less on adherence to specific medications. Of the little that is known, only 33% of patients prescribed duloxetine were considered highly adherent, with a higher adherence to lower dosages. When compared to pregabalin, duloxetine had better adherence rates with less titration of dosage during the first year.

It is of utmost importance to investigate adherence in fibromyalgia, addressing the many issues that affect it in order to better our practice. Addressing compliance and adherence, particularly in these patients, might lead to reduced health care costs and improved quality of care. More data on this issue are therefore warranted.

References

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Evolution of Ebola virus over time
The high rate of mortality in the current Ebola epidemic has made it difficult for researchers to collect samples of the virus and study its evolution. Gire et al. describe Ebola epidemiology on the basis of 99 whole-genome sequences, including samples from 78 affected individuals. The authors analyzed changes in the viral sequence and conclude that the current outbreak probably resulted from the spread of the virus from central Africa in the past decade. The outbreak started from a single transmission event from an unknown animal reservoir into the human population. Two viral lineages from Guinea then spread from person to person into Sierra Leone.

Science 2014; 345: 1369
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Loss of oncopgenic Notch1 with resistance to a PI3K inhibitor in T cell leukemia
Mutations that deregulate Notch1 and Ras/phosphoinositide 3 kinase (PI3K)/Akt signaling are prevalent in T cell acute lymphoblastic leukemia (T-ALL), and often coexist. Dail and colleagues show that the PI3K inhibitor GDC-0941 is active against primary T-ALLs from wild-type and KrasG12D mice, and addition of the MEK inhibitor PD0325901 increases its efficacy. Mice invariably relapsed after treatment with drug-resistant clones, most of which unexpectedly had reduced levels of activated Notch1 protein, down-regulated many Notch1 target genes, and exhibited cross-resistance to γ-secretase inhibitors. Multiple resistant primary T-ALLs that emerged in vivo did not contain somatic Notch1 mutations present in the parental leukemia. Importantly, resistant clones up-regulated PI3K signaling. Consistent with these data, inhibiting Notch1 activated the PI3K pathway, providing a likely mechanism for selection against oncogenic Notch1 signaling. These studies validate PI3K as a therapeutic target in T-ALL and raise the unexpected possibility that dual inhibition of PI3K and Notch1 signaling could promote drug resistance in T-ALL.

Nature 2014; 513: 512
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“Quality is never an accident. It is always the result of intelligent effort”
John Ruskin (1819-1900), leading English art critic of the Victorian era, also an art patron, draughtsman, watercolorist, a prominent social thinker and philanthropist. Today, his ideas and concerns are widely recognized as having anticipated interest in environmentalism and sustainability