Predicting fibromyalgia, a narrative review: Are we better than fools and children?

J.N. Ablin¹, D. Buskila²

¹ Institute of Rheumatology, Tel Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Israel
² Department of Medicine, H. Soroka Medical Center and Faculty of Health Sciences, Ben Gurion University of the Negev, Be’er Sheva, Israel

Abstract

Fibromyalgia syndrome (FMS) is a common and intriguing condition, manifest by chronic pain and fatigue. Although the pathogenesis of FMS is not yet completely understood, predicting the future development of FMS and chronic pain is a major challenge with great potential advantages, both from an individual as well as an epidemiological standpoint. Current knowledge indicates a genetic underpinning for FMS, and as increasing data are accumulated regarding the genetics involved, the prospect of utilizing these data for prediction becomes ever more attractive. The co-existence of FMS with multiple other functional disorders indicates that the clinical identification of such symptom constellations in a patient can alert the physician to the future development of FMS. Hypermobility syndrome is another clinical (as well as genetic) phenotype that has emerged as a risk factor for the development of FMS. Stressful events, including early life trauma, are also harbingers of the future development of FMS. Functional neuroimaging may help to elucidate the neural processes involved in central sensitization, and may ultimately also evolve into markers of predictive value. Last but not least, obesity and disturbed sleep are clinical (inter-related) features relevant for this spectrum. Future efforts will aim at integrating genetic, clinical and physiological data in the prediction of FMS and chronic pain.

1. Introduction

The Merriam-Webster dictionary defines ‘prediction’ as ‘a statement about what will happen or might happen in the future’. Hence, although it appears unambiguous that predicting deals with the future, the term encompasses both things that will in fact happen, as well as those which only might happen. Predicting is not a full-proof business and medical prediction is no exception. Nonetheless, predicting future development of disease has obvious practical advantages, both on an individual and a community level. Accurately anticipating who (as well as how many) will develop a future medical condition could be a critical step towards developing effective preemptive strategies aimed at prevention. In the current review we have attempted to describe what knowledge has been achieved through various and far-flung lines of medical evidence, regarding predicting the development of the fibromyalgia syndrome (FMS), a fascinating and unique clinical entity affecting a significant proportion of the population at large.

FMS is one of the most challenging and enigmatic conditions confronting those dealing with chronic pain. Although it is currently recognized as an extremely common disorder with prevalence rates ranging at 2–3% of the population (Ablin et al., 2012; Vincent et al., 2013), the pathogenesis remains incompletely understood and the strategies of treatment fall short of the perfect remedy hoped for by patients. Although considerable amounts of evidence have been collected over the recent years regarding effective (and less effective) treatments for FMS, clinical improvement as a result of treatment is often partial at
best and FMS patients continue to suffer from considerable symptoms, as well as reduced function and quality of life. The economic costs of FMS, both direct and indirect, are also huge (Knight et al., 2013). Thus, although the search continues for more effective and cost-effective treatments for FMS (Ablin and Buskila, 2013), prevention would undoubtedly also be something of a holy grail waiting to be found. Notably, at the current point of our incomplete understating, the area of prevention is all but non-existent. It is in this context that identifying factors capable of predicting the development of FMS become important. Identifying individuals who are prone to developing FMS could alert physicians to the possibility of early detection, preventing unnecessary, deleterious, prolonged and misguided investigations. It could cut costs and increase the chance of a positive response to treatment. Optimally, it might lead to the development of actual preventive measures, which might be directed at these individuals in the hope of preventing the progression towards full-blown, chronic FMS.

2. Predicting on the basis of our genes

2.1 Familial and genetic background of FMS

FMS is a disorder predicated on altered function of the central nervous system (CNS) (Woodman, 2013). Like all other functions of the CNS, the manner in which pain is processed and transmitted throughout the nervous system is determined by a variety of genetic factors. Thus, it comes as no surprise that a genetic underpinning for FMS is widely assumed (Ablin et al., 2008). This assumption is strongly supported by the finding of clear familial aggregation in FMS (Arnold et al., 2004). In light of these findings and assumptions, a long line of research has focused on searching for genetic determinants of FMS, using both target gene (Lee et al., 2012a; Smith et al., 2012) and more sophisticated genome-wide approaches (Arnold et al., 2013).

Since increased pain processing of pain in the CNS in FMS is considered to involve aberrant function of a significant number of neurotransmitters that participate in pain modulation, e.g., serotonin, norepinephrine (Schmidt-Wilcke and Clauw, 2011), genes related to these players were targeted as early candidates in the search after genetic associations in FMS.

Among these targets, serotonin transporter (5-HTT), the gene-linked polymorphic region (5-HTTLPR) S/L allele (Offenbaecher et al., 1999a; Cohen et al., 2002), the catechol-O-methyltransferase (COMT) val158Met (Cohen et al., 2009) and the 5-HT2A receptor 102T/C polymorphism (Bondy et al., 1999) have been repeatedly studied.

2.2 Can genetic markers predict the development of FMS?

As demonstrated recently through a meta-analysis of the studies on these genetic markers (Lee et al., 2012b), the 5-HT2A receptor 102T/C polymorphism appeared to confer susceptibility to FMS, whereas the other two markers failed to show such an association.

Genes that are responsible for pain sensitivity may participate in determining susceptibility to chronic pain. Previous studies have demonstrated associations between functional polymorphisms and pain sensitivity for several genes, including GCH1 (Tegeder et al., 2006, 2008; Campbell et al., 2009) and OPRM1 (Fillingim et al., 2005; Shabalina et al., 2009). In a subsequent study Holliday et al. (2009) failed to demonstrate an association between these genes and the frequency of chronic widespread pain. Diatchenko et al. (2005) were the first to demonstrate that genetic
variants (haplotypes) of the gene encoding COMT could predict the development of chronic temporomandibular joint disorder, a condition closely associated with FMS (Hoffmann et al., 2011). This study emphasized the possibility that genetic variations influencing the function of the sympathetic nervous system could have an important role in determining the likelihood of developing chronic pain. Vargas-Alarcon et al. (2007) were able to demonstrate an association between the COMT haplotype and the occurrence of FMS in a sample of Spanish patients, with a much weaker association among Mexican individuals.

In another large population-based study, Hocking et al. (2010) investigated the role of both the beta-2-adrenergic receptor as well as the COMT mutations in predisposing to chronic widespread pain. In this study nine single nucleotide polymorphisms (SNPs) were examined across ADRB2 and 11 SNPs across COMT. Although specific SNPs in the ADRB2 gene were associated with pain status and severity, no association was found between SNPs in the COMT gene and pain.

The voltage-gated sodium channel type IX α subunit, (Nav1.7) encoded by the SCN9A gene, has been associated with a spectrum of human genetic pain disorders including primary erythermalgia and paroxysmal extreme pain disorder as well as channelopathy-associated insensitivity to pain (Drenth and Waxman, 2007).

Genetic variations in the SLC6A4 gene affecting the serotonin system have been associated with facilitation of experimental pain, as well as with increased risk for chronic widespread pain (Lindstedt et al., 2011a,b). Similarly, variations of the HTR2A gene, also affecting serotonin, have also been associated with both an increase in post-surgical pain, as well as an increase in chronic widespread pain (Aoki et al., 2010; Nicholl et al., 2011).

As in many other fields in which genetic information has been harnessed for evaluation of clinical conditions, the field of pain is also evolving from the era candidate gene association studies towards that of genome-wide association studies (GWAS). Thus, Anttila et al. (2010) have shown a link between the minor allele of rs1835740 on chromosome 8q22.1 and the risk for migraine pain. Recently, Arnold et al. (2013) have used a genome-wide linkage scan in order to identify susceptibility loci for FMS. Individuals from 116 families were genotyped with 341 microsatellite markers. In this study, two markers located on chromosome 17p11.2–q11.2 were found to be linked with FMS. Notably, the chromosome 17p11.2–q11.2 region coincides with the map coordinate for two potential FMS candidate genes, the serotonin transporter gene (SLC6A4) (Offenbaecher et al., 1999b) and the transient receptor potential vanilloid channel 2 gene (TRPV2) (Mandadi and Roufogalis, 2008; Broad et al., 2009). Although both of these genes have been associated with the control of pain and the occurrence of FMS, it must be noted that an area such as that identified contains more than 100 other genes as well. Thus, evidently much more research is necessary before determining the precise role of such chromosomal areas in the pathogenesis of FMS.

Experience gathered in other complex medical conditions indicates that despite progress made in GWAS, most variants identified so far confer relatively small increments in risk, and explain only a small proportion of familial clustering (Manolio et al., 2009).

Concluding this section, although genetics are yet insufficient for the precise prediction of FMS, great progress has been made along this path; thus, the prospect of future prediction of FMS based on genetic diagnosis appears to be a plausible and promising avenue.

3. Clinical-predicting factors: the functional syndrome cascade

Functional somatic syndromes (FSSs) are a spectrum of clinical entities, which are recognized as frequently co-appearing in the same individuals. Many clinical characteristics are common to these conditions, including over-representation among women, lack of specific diagnostic laboratory of imaging findings, exacerbation with stress, as well as during menstruation and the absence of specific pathological findings in the symptomatic organs (Henningsen et al., 2007). CNS sensitization has been proposed as being the basic underlying mechanism unifying these diverse clinical conditions, which in addition to FMS include irritable bowel syndrome (IBS), chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome and many more (Yunus, 2007, 2008). Warren et al. (2013) have recently demonstrated that the number of existing FSSs is an important risk factor for new different FSSs, including FMS. In this study, an individual with three or more antecedent FSSs had almost five times the odds of developing an FSS compared with an individual with no antecedent FSS. This finding obviously can alert the clinician dealing with patients exhibiting what appear to be functional somatic symptoms to the very real possibility of additional symptoms and syndromes subsequently developing in the same patient. Moreover, the clinician should remain vigilant for
such developments and actively inquire about symptoms that may go unreported.

4. Be flexible (but not too flexible) – the role of hypermobility

Joint hypermobility is a common and frequently overlooked genetic disorder (Fikree et al., 2013), often considered to overlap with the Ehlers–Danlos syndrome, hypermobility type. Once considered to represent a benign variation in connective tissue qualities, the syndrome has gained recognition as a multisystem disorder associated with chronic widespread pain, dysautonomias and gastrointestinal dysmotility. Gedalia et al. (1993) recognized the strong association between joint hypermobility and FMS in children. Thus, it currently appears that joint hypermobility should be considered a special case, in which a genetic risk factor for FMS carries with it a distinct and easily recognizable phenotypic expression.

5. Early stress, late pain: The effect of early life events

Although stress, in general, and early life distress, in particular, are widely considered to be potential triggers for the development of FMS, the actual causal relationship is complex (Ablin and Clauw, 2009). A number of population-based studies have examined the psychological predictors of chronic regional or widespread pain in the United Kingdom. These studies have examined the temporal and longitudinal relationship between distress and pain, thus implying cause and effect, rather than the cross-sectional relationship (which may identify distress due to pain rather than causing pain). These studies have shown that individuals with high baseline levels of psychological distress are more likely to develop subsequent chronic regional or widespread pain [odds ratio (OR) 1.5–2.0] (Croft et al., 1996; McBeth et al., 2001, 2002; Papageorgiou et al., 2002). At the same time, having baseline chronic pain is a strong factor predicting future psychological distress (OR 3–5).

Ongoing stress has been demonstrated to be associated with chronic pain in a variety of models and situations. Thus, the ongoing threat of cross-border missile fire has been associated with an increased prevalence of pain and related symptoms in an Israeli town (Ablin et al., 2010a). Similarly, stress associated with workplace bullying has been associated with FMS (Kivimaki et al., 2004). Although it is difficult to accurately quantify, the stress of childhood sexual trauma has also been linked with FMS (Hauser et al., 2011), and increased rates of FMS have been observed among holocaust survivors many decades later (Ablin et al., 2010b). These observations imply that stress-related neuroplastic changes may be a slowly developing and chronic process.

Baseline function of the stress response, e.g., the hypothalamic-pituitary-adrenal (HPA) axis, is also a predictor of chronic widespread pain, independent of distress and other psychological factors (McBeth et al., 2007).

6. Can functional neuroimaging predict the transition to chronic pain?

Great progress has been made over the last decade in understanding the pathophysiological nature of FMS through the implementation of functional neuroimaging technology. Thus, Gracely et al. (2002) were the first to use this tool in order to demonstrate objectively an increase in activation of pain processing centres in the CNS in FMS patients. Although this approach has done much to further our understanding of the mechanisms underlying FMS (e.g., the central sensitization paradigm), it has not been until very recently that researchers have used it in order to try and predict the transition from acute to chronic pain. Currently, however, evidence has started to emerge indicating that the transition from acute to chronic pain may be accurately anticipated by imaging, including both functional and structural connectivity at the time of (acute) presentation. Thus, Baliki et al. (2012) were able to show that, initially, greater functional connectivity of nucleus accumbens with prefrontal cortex predicted pain persistence, implying that corticostriatal circuitry is causally involved in the transition from acute to chronic pain. In addition, researchers were able to discover brain white matter structural abnormalities, as measured by diffusion tensor imaging, which accurately predicted pain persistence over the next year (Mansour et al., 2013). Taken together these results imply that advanced imaging technology may evolve in the foreseeable future into a practical tool in predicting the development of chronic pain states, including FMS.

7. Can body mass index predict pain?

Obesity and overweight have long been recognized as risk factors for the development of various local painful musculoskeletal conditions such as osteoarthritis of the knee. The possibility of a link between obesity and the development of FMS has only more recently gained attention both in adolescence (Deere
et al., 2012) and in adults (Ursini et al., 2011). Many mechanisms may be involved in this association including decreased physical activity (which appears to be an independent risk factor for FM), hormonal influences such as hypothyroidism and menopause, sleep disturbances and more. Thus, while it is difficult to determine the causality of the relationship it appears prudent to maintain vigilance regarding the possibility of chronic pain, as well as FMS, developing in obese individuals.

Physical exercise remains one of the most documented and effective treatment modalities for FMS (Busch et al., 2007, 2008). Thus, it is not surprising to discover that FMS patients often tend to spend a high proportion of waking hours in sedentary activities (Ruiz et al., 2013). An interesting study by Glass et al. (2004) has even demonstrated that ‘exercise deprivation’, i.e., the cessation of exercise by regularly exercising, asymptomatic, healthy adults, led to the development of FMS-like symptoms such as pain, fatigue and mood disorders. Most interestingly in this study, those individuals developing symptoms differed from those who did not in baseline measures of HPA axis, immune and autonomic function. Thus, a subset of healthy individuals who have hypoactive function of the biological stress response systems may be at risk for developing chronic multisymptom including FMS, especially when some form of trauma interferes with their regular routine of physical activity.

8. Sleep problems and pain

Disturbed patterns of sleep were recognized very early in the history of the modern awareness of FMS (Moldofsky, 1989, 2001), and specific sleep disturbances such as alpha wave intrusion were recognized as typical of the FMS presentation (Roizenblatt et al., 2001). Frequent awakening, non-restorative sleep and chronic fatigue are considered to represent integral components of the FMS spectrum (Theadom et al., 2007; Bigatti et al., 2008). In a recent study, Mork and Nilsen performed a longitudinal observation after 12,350 female individuals not suffering from symptoms of FMS at baseline. At follow-up 11 years later, 327 individuals had developed FMS and a dose-dependent association was found between sleep problems and risk of FMS, with an adjusted risk ratio of 3.43 (Mork and Nilsen, 2012). This finding is in accordance with the anecdotal report of FMS patients, who often report that sleep disturbances existed long before the appearance of pain. Thus, a persistently disturbed pattern of sleep is another clinical clue that should alert the physician to the possibility of subsequent FMS.

Utilizing a retrospective electronic medical record analysis, Silverman et al. have recently attempted to identify clinical predictors of FMS diagnosis. Using a logistic regression, a comparison was performed between 2823 individuals with a FMS diagnosis and 210,495 individuals without such a diagnosis. The model identified 17 variables significantly associated with FMS diagnosis, including the number of pain medication prescriptions, the number of musculoskeletal pain conditions, the presence of gastrointestinal and sleep disorders, and the number of outpatient visits and hospitalizations (Silverman et al., 2013). This study represents a systematic epidemiological approach towards the prediction of FMS based on clinical parameters.

9. Conclusion

FMS is a complex symptom-defined clinical entity, the pathogenesis of which is only partly understood. Accurately predicting the future development of such a condition in the individual patient is obviously a challenging endeavour. Although some patients may present with a range of clinical characteristics that clearly point towards the spectrum of FSS, e.g., IBS, chronic fatigue, and thus may alert an astute clinician to the risk of FMS, in other cases the risk may be far more subtle. Hypermobility (with or without dysautonomia) is a unique genetically based phenotypic trait that can draw attention to the risk of chronic pain and FMS. The routine clinical application of other recognized genetic risk factors is not yet available but holds promise for future risk stratification. Other clinical clues such as obesity and disturbed sleep are useful to keep in mind. Sophisticated techniques of functional neuroimaging may eventually shed additional light both on the pathogenesis of FMS and on the transition towards chronic pain.

References


