Review

Fibromyalgia in patients with breast implants: an environmental trigger?

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ABSTRACT

Fibromyalgia (FM) is a heterogeneous condition of unclear pathogenesis. Recently, silicone breast implants (SBI) have been implicated as potential triggers for FM. Patients with breast implants may develop fatigue, diffuse joint and/or muscle pain, and brain fog, in addition to symptoms of dysautonomia such as sicca symptoms, pyrexia, and/or postural orthostatic tachycardia syndrome (POTS). In 1999, it became evident that patients with SBI related illness develop identical symptoms to those with idiopathic fibromyalgia (FM) suggesting that SBI-associated FM is not an unrecognised new disease. Importantly, however, patients with SBI-associated FM may substantially improve after the removal of explants; whereas those with idiopathic FM, in general, do not recover. Hence, prompt recognition of SBI-associated FM is critical for improving patient quality of life. In the current paper, we review the recent data that supports the scientific evidence of the existence of SBI-associated FM and propose how it can be differentiated from idiopathic FM. Based on the evidence that SBI may trigger FM, we postulate that also other environmental factors may be involved in the pathogenesis of FM.

Introduction

Chronic widespread pain due to fibromyalgia (FM) is one of the most prevalent musculoskeletal illnesses in women and it has been suggested that up to 13% of women may suffer from FM (1). Although it can affect people of any age, FM is most commonly diagnosed in women of 30-35 years. A diagnosis of FM is not based on pathological findings or conventional medical investigations, but the diagnosis can be made based on a diagnostic questionnaire (2). The patients' burden of the disease is profound, and their healthcare use is extensive. As a result, societal costs are substantial (3). Unfortunately, many patients have difficulties to get a diagnosis, receive information, and have regular follow-up. This conflicts with the international guidelines for FM management, which stress the importance of prompt diagnosis, sufficient patient information, thorough pain assessment, and regular follow-up (4). In fibromyalgia, pharmacological treatments should be based on the expected benefits and evaluation of side effects, with non-pharmacological modalities also being considered of importance.

Breast implants, breast implant illness, and fibromyalgia

The global market for medical implants in general exceeds 100 billion USD in revenues, with at least 2 billion USD spent on breast implants. It is estimated that about 2–4% of adult women in the Western world have breast implants (5, 6). Roughly, 70% of these are utilised for cosmetic reasons and 30% are utilised for reconstruction after mastectomies. Silicones are synthetic polymers that have been utilised for nearly 60 years for a variety of medical reasons (7). When silicones were introduced, they were initially thought to be biologically inert and were incorporated in a variety of medical devices such as joints, artificial heart valves, drains, shunts, and even catheters. However, it quickly became apparent that the use of silicone-related medical devices was associated with the development of a variety of inflammatory diseases (7, 8). In genetically susceptible individuals, exposure to silicone results in localised

sensitisation and systemic reactions stemming from "leakage" of silicone to remote areas. These systemic reactions can result in inflammatory changes that are specific, such as the generation of anti-silicone antibodies and/or anti-collagen antibodies (9, 10); and more generalised symptoms such as pain and fatigue. Indeed, silicones have been utilised to augment experimental pre-clinical animal models for a variety of inflammatory diseases such as lupus and collagen-induced arthritis (11, 12). Further to that, several autoimmune diseases have been linked to silicone exposure in humans such as Sjögren's syndrome and systemic sclerosis (13). Intriguingly, these diseases are commonly associated with fibromyalgia (FM), which is characterised by severe, debilitating, and relentless diffuse muscle and/or joint pain (14-16). In other words, there is a growing amount of evidence that directly implicates silicones as having significant complications.

Silicone breast implants (SBI) are considered to be high risk medical devices associated with short term and long-term sequelae (17). For instance, in a recent paper summarising the outcomes of revision surgeries after breast implant surgery as registered in four different countries (Australia, the Netherlands, Sweden, and the USA), it was found that the incidence of revisions within 2 years after surgery was 6.5–15.8% for primary breast reconstruction and 1.6 -3.5% for primary breast augmentation (18, 19).

Thus, immediate complications (<2 year after surgery) include:

a. local surgical complications such as pain, swelling, infections, and/or skin necrosis;
b. local inflammation resulting in capsular contracture or implant rupture;
c. allergies to components of the breast implants causing a localised contact dermatitis (20, 21);

More delayed complications include: a. Silicone migration to distant areas; b. SBI-related malignancy; c. SBI-related autoimmunity; d. SBI-related dysautonomia [also called: "breast implant illness" (BII) or "autoimmune/inflammatory syndrome by adjuvants due to silicone incompatibility" (ASIA)].

Silicone migration to distant areas has been documented in the lungs, skin, lower extremities, and/or other parts of the body since 1978 (7, 22). In addition, at autopsy, silicone gel "bleed" is found throughout the whole body including the brain (23). Silicone migration may occur either after breast implant rupture or due to silicone leakage from intact breast implants. To overcome systemic bleeding of silicones, cohesive implants were developed in 1994. However, it recently became clear that migration of silicones also occurs from cohesive implants (22, 24). The increased risk for lymphoma development in patients with SBI patients has been well documented (6, 17). Most particularly, the risk to develop an anaplastic large T-cell lymphoma (ALCL) of the breast, negative for anaplastic lymphoma kinase-1 (ALK-1) but positive for CD30 is strongly increased [Odds Ratio: 421.8; 95% CI, 52.6 – 3385.2) (6, 25, 26). It has been postulated that chronic activation of the immune system by the silicones and/or the biofilm around the implants results in the development of these lymphomas (25). In addition, patients with silicone breast implants may develop other forms of non-Hodgkin lymphomas such as Epstein-Barr virus-positive large B cell lymphoma and/or intravascular large B-cell lymphoma (27). Moreover, the FDA recently issued a safety communication stating that squamous cell carcinoma linked to breast implants also occurs (28).

Specific autoimmune diseases are more common in patients with silicone breast implant (*e.g.*, Hashimoto's thyroiditis, systemic sclerosis, sarcoidosis, and/or Sjögren's syndrome). This observation is supported by several epidemiologic studies evaluating the frequency of autoimmunity in patients with silicone breast implants (7, 13, 17, 29-34). In 2016, Balk *et al*. found an increased risk for rheumatoid arthritis and Sjögren's syndrome when systematically reviewing the literature (1980-2016) regarding long-term outcomes in SBI patients (35). But while performing the systematic review, the authors concluded that the studies that were performed were of rather low quality and did not provide conclusive evidence regarding the safety -or otherwise- the unsafety of SBI. Consequently, we performed a study in 2018, which included 24,651 women with SBI and 98,604 matched SBI-free women. We calculated that women with breast implants had a 45% increased risk of being diagnosed with at least one autoimmune/rheumatic disorder, compared to those without breast implants (13). The strongest associations recorded were for Sjögren's syndrome, systemic sclerosis, and sarcoidosis. It is, however, important to realise that geographical differences exist in the occurrence of autoimmune diseases, which may stem from the fact that HLA alleles are differentially distributed in populations around the globe (36).

Additionally, the prevalence of vitamin D insufficiency differs worldwide. This is important as studies have shown an association between the development of various autoimmune diseases and vitamin D deficiency (37).

Symptoms of patients that present with BII (Fig. 1) can be subdivided into 3 categories (17): i. neurological/musculoskeletal manifestations (*e.g.*, arthralgia, myalgia, POTS, cognitive dysfunction); ii. immunological manifestations (*e.g.*, autoantibody generation and/or impaired B cell differentiation); iii. vascular manifestations (*e.g.*, Raynaud's phenomenon, livedoid rashes).

Fatigue and widespread pain are the most common symptoms associated with BII (7, 17). Most BII patients develop chronic and debilitating symptoms that satisfy the classification criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and/or fibromyalgia (FM) (2, 38). In addition, about 60% of BII patients have scores indicative of cognitive impairment (39). Patients often present with tenderness throughout their body, widespread pain, joint stiffness and tingling sensations in their arms and legs. Pain and burning sensations often start in their feet and advance proximally; symptoms that are due to small fibre neuropathy. Other consistent symptoms that are present in most

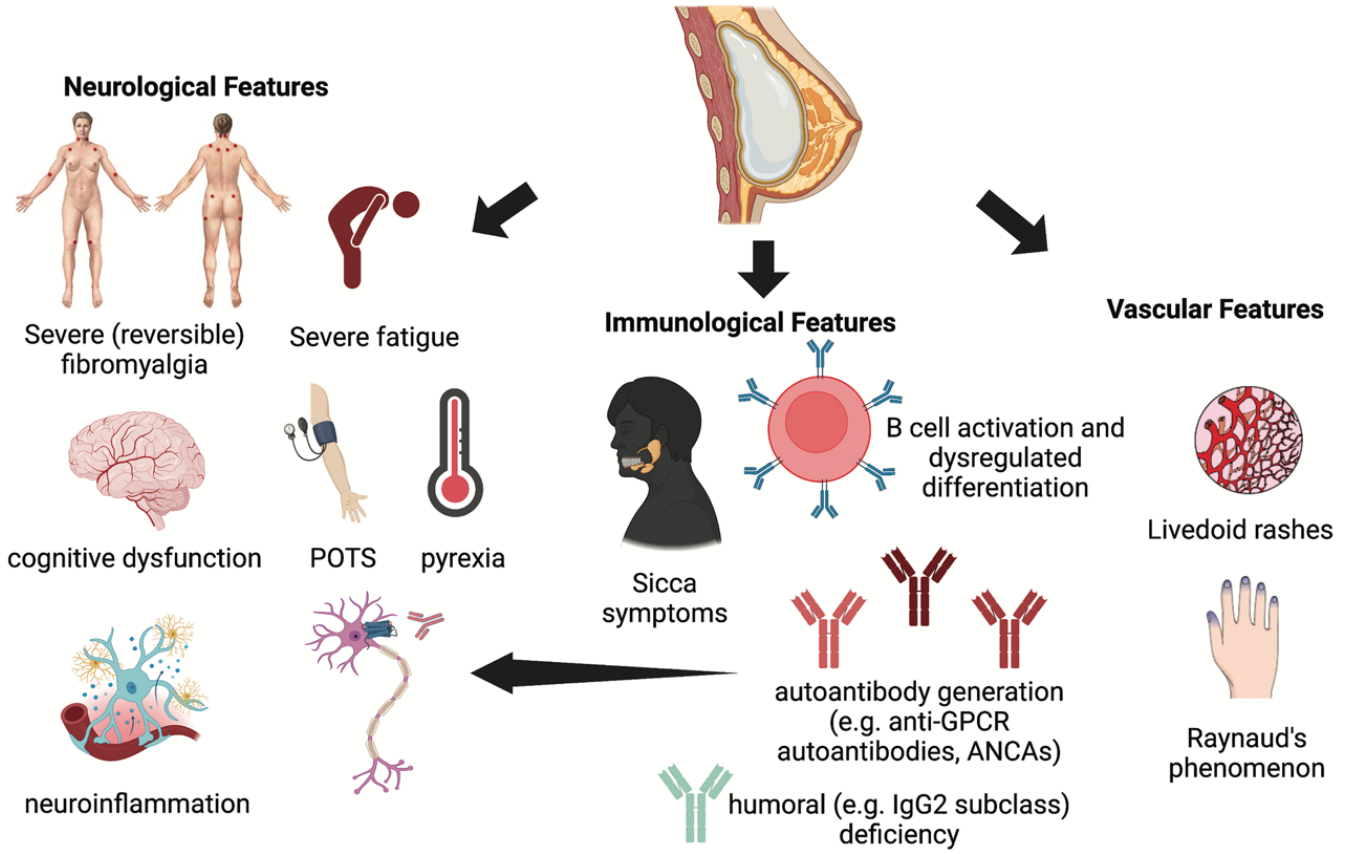

Fig. 1. Clinical features of silicone breast implant associated fibromyalgia.
POTS: postural orthostatic tachycardia syndrome; GPCR: G-protein coupled receptors; ANCA: anti-neutrophil cytoplasmic antibody. Created with Biorender.com.

patients are pyrexia, dry eyes, and a dry mouth. Furthermore, patients report an increased occurrence of allergies and upper respiratory tract infections. Finally, many patients experience signs of a postural orthostatic tachycardia syndrome, (livedoid) rashes and Raynaud's phenomenon (7).

In 1995, Bridges postulated that patients with breast implants who developed arthralgias, myalgias, ocular dryness, paraesthesia, and cognitive impairment suffered from a new disease (40). Further to that, Wolfe (41) noted that patients with SBI-associated FM were indistinguishable from those with idiopathic FM. In FM, several environmental factors such as climatic variations, pollution, and infections have been demonstrated to influence disease manifestations and intensity (42). In addition, it has been postulated that physical and emotional stress induce dorsal root ganglia inflammation resulting in the chronic widespread pain that FM patients suffer from (43). In the current manuscript, we will discuss another environmental factor, *i.e.*, silicone breast implants.

Importantly, however, in contrast to idiopathic FM, SBI-associated FM is often reversible with the removal of the implants (27). Clinically, several critical factors may help clinicians better identify patients at risk for developing SBI-associated FM (7). First, patients with a known history of atopic disease (*e.g.*, eczema, asthma, allergic rhinitis) are at increased risk for developing severe pain following SBI. Second, patients with a known history of autoimmune diseases or a family history of these diseases are also at increased risk. Hence, genetic and/or epigenetic factors that are known to promote atopic and/or inflammatory diseases may increase the risks for developing these syndromes. These include the presence of a common human leukocyte haplotype (HLA), and epigenetic factors such as insulin resistance, obesity, and exposure to smoking (31, 44 -47). Other emerging risk factors may include specific forms of immune deficiency, that are associated with the development of inflammatory diseases (*e.g.*, IgG2 subclass deficiency) (48).

Is FM in patients with breast implants an epiphenomenon?

Although it has been repeatedly reported that the quality of life associated with pain in patients with SBI-associated FM drastically improves (or resolves) after explantation, the causality that breast implants can trigger FM continues to be debatable by many physicians - particularly in the plastic surgery literature (49-51).

Further to this, SBI-associated FM is not considered to be separate from idiopathic FM as it does not have a separate international classification of disease (ICD) code. Together, these factors make it challenging to describe its toll on society. This includes the incidence of SBI-associated FM in specific at risk populations, using administra-

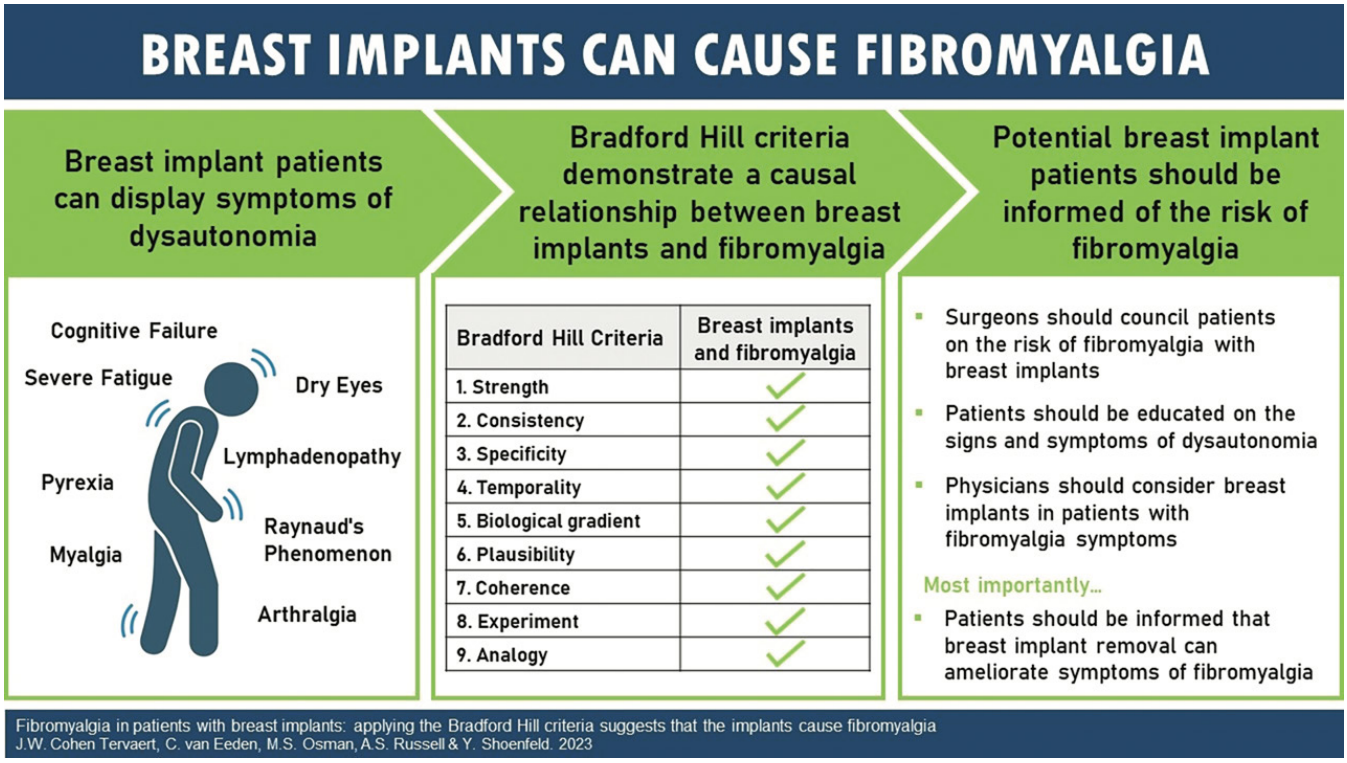

Fig. 2. Fibromyalgia in patients with breast implants: applying the Bradford Hill criteria suggests that the implants cause fibromyalgia. (Cohen Tervaert JW, van Eeden C, MOsman MS, Russell AS, Shoenfeld Y. 2023).

tive data research methodologies, the prevalence of the disease, as well as the economic toll it may have caused. Causation is often an interpretation, rarely a discrete fact (52). Outside of infectious or genetic diseases, causation is rarely "established". This is especially true for immune-mediated diseases as there are many factors at play, genetics, evolving epigenetic exposures, and heterogeneous populations. In 1965, Dr. Austin Bradford Hill developed criteria to evaluate causal inference between an environmental exposure and a certain disease (53). These criteria were utilised to establish a causal link between smoking and lung cancer. Bradford Hill reported in 1950 that the risk of lung cancer was 25 times higher in those who smoked >25 cigarettes per day compared to people who never smoked. Although a causal relation between smoking and lung cancer seemed likely, a debate between epidemiologists and statisticians started (54) and only in 1965, could Bradford Hill end the discussion by defining nine criteria (nowadays called the Bradford Hill criteria). Based on existing data, we will evaluate the scientific evidence that SBI may be a direct cause for FM (Fig. 2).

Bradford Hill criteria for causation

Strength of the association

Cohort studies that have looked at breast implants and dysautonomia symptoms clearly described an association (17). In addition, great weight is generally given to "*N-of-1* trials" that employ "challenge-dechallenge-rechallenge" strategies to derive evidence. Reports in the published literature on breast implants, which includes both case reports and larger observational studies, demonstrate that symptoms such as widespread pain begin after breast implant placement, and resolve in a great many patients after removal (27, 55). In 2017 de Boer *et al*. (55) reviewed case reports and case series and found that 469 of 622 (75%) of SBI patients described improvement after explantation. During the last six years it has been reported that over 2000 SBI patients have undergone breast implant removal. Symptoms improved in 50–98% of patients (27) although complete disappearance of symptoms occurs only rarely (56). In patients with persisting symptoms, treatment with duloxetine, low dose naltrexone, dietary modifications, and vitamin D and melatonin supplementation often ameliorate disease manifestations.

Some patients with SBI-associated FM do not undergo a removal of their breast implants. Reasons for not explanting are among others: costs, finding a plastic surgeon who is willing to remove the breast implants, poor health, and/or cosmetic reasons (57). In the patients without an explantation improvement of symptoms occurs in less than 15% of women (27). In recent studies, 70–80% of patients evaluated for SBI-associated complaints had symptoms suggestive of FM (57-59). Also, similar observations can be found in the manufacturer and user facility device experience (MAUDE) database of the FDA (60). In addition, it has been demonstrated in two series that the relapse risk is high (about 50%) after rechallenge (that is after placement of a new breast implant after explantation). In contrast, the relapse rate of SBI-associated FM is low when no reconstruction with new breast implants is performed (< 20%) (27, 61).

Consistency of association
In most patients with SBI-associated FM, a consistent group of dysautonomia symptoms are generally present (30). Notably, most symptoms ameliorate after explantation. So, challenge-dechallenge studies have resulted in a similar type of evidence in women from ethnically diverse groups performed by different independent investigators from different countries (17, 27, 30). In the Netherlands, USA and Brazil a comparable improvement of symptoms such as widespread pain has been reported after explantation (62-64).

Specificity of association
In SBI-associated FM, patients present with a cluster of symptoms consistent with the same classification criteria, which have been determined *a priori*. Together, these observations provide external validation for these classification criteria. This is highlighted by the observation that nearly all patients present with ME/CFS, FM, sicca, pyrexia and cognitive impairment. So, patients have a predictable cluster of symptoms that is reproducible across various populations (50, 60, 65, 66). Importantly, improvement of pain symptoms occurs in 50-98% of explanted patients, whereas in patients that refuse explantation, less than 15% improve (27, 58).

Temporal relationship with the exposure to SBI
Dysautonomia symptoms appear for the first time after breast implantation and often improve and/or disappear after explantation (55, 62-64). Improvement of symptoms is less likely to occur when the duration of implantation increases (27). For instance, it was recently reported that the likelihood for improvement was clearly lower in women who had their implants for over 10 years compared to those women who had their implants removed within 10 years after implantation (56). This suggests that the duration of exposure is related to outcome.

Biological gradient of response following explantation
Improvement of dysautonomia symptoms is more likely to occur when the explantation is performed within 10 years after implantation (*vide supra*). So, this suggests that the duration of exposure to gel bleed and increasing amounts of gel bleed over the years is related to outcome.

Biological plausibility of the association
The implantation of any biomaterial results in an inflammatory and fibrotic response. Although biomaterials are, generally, non-toxic and non-immunogenic, a foreign body reaction (FBR) is always triggered. Furthermore, microbial biofilms are formed on the implants, contributing to the chronic inflammatory response and as a result the degree of fibrosis will dramatically increase (27). After implantation, the sticky silicones bind to proteins which adsorb to the surface of the implants. In a recent study of seven patients who were undergoing a mastectomy and subsequently placement of tissue expanders with a polydimethyl siloxane elastomer shell, daily samples were collected of the wound from day 1 to day 5, and devices were studied that were removed between 24 and 28 weeks after implantation to study the SBI-adsorbed immunoreactive proteome (67).
Inter-individual variability was high. Intraindividual comparison was therefore crucial. 895 common-plasma-derived wound proteins were demonstrated. Most proteins were secretion products of neutrophils and/or monocytes, and products of the complement and coagulation cascade. Apart from attraction of neutrophils and monocytes, mast cells and macrophages are attracted contributing to a fibrotic response. In a recently described humanised mouse model to test the development of FBR, it was demonstrated that depletion of phagocytes results in a complete loss of FBR, demonstrating that macrophages are pivotal for the development of fibrosis after biomaterial implantation (68). The macrophages that are attracted are predominantly of the pro-inflammatory M1 subtype and the attraction of these macrophages to the biomaterial is critically dependent on recruitment of mast cells and liberation of histamine (17). Upon activation of the macrophages, proinflammatory cytokines such as IL-6, TNF-alpha and IL-1 are produced, and T cells migrate to the implant and release pro-inflammatory and pro-fibrotic mediators resulting in the differentiation of fibroblasts to myofibroblasts resulting in overproduction of extracellular matrix proteins, fibrotic responses and capsular contracture. Since regulatory T cells are diminished and since their numbers are inversely proportional to the degree of fibrosis, a strong Th1/Th17 immune response is induced. Importantly, it has been recently demonstrated that the topography of the breast implant influences the extent of the immune response and the extent of the biofilm formation (68).
SBI can serve as adjuvants which promote chronic stimulation of both the innate and adaptive immune system resulting in the production of autoantibodies and a localised inflammatory microenvironment (69). Adjuvants were first described in 1924 by Ramon as a substance that causes a more robust immune response when used in combination with a specific antigen than when the antigen is used alone (70). Adjuvants employ the following mechanisms to enhance immune responses: i. Sustained release of antigens; ii. Up-regulation of chemokines and cytokines; iii. Cellular recruitment; iv. Increase of antigen uptake; v. Promoting antigen migration to draining of lymph nodes. It has been demonstrated that inflammasomes are involved in the mechanisms of adjuvant action. By sensing cellular debris and silicones after SBI implantation, a nucleotide oligomerization domain (NOD)-like receptor, the pyrin-domain-containing 3 (NLRP3) receptor, activates cryopyrin (or NALP3) inflammasomes. After these steps, antigen-specific B and T cells are activated resulting in autoantibody production and secretion and the formation of effector CD8 T cells (71). More recently it was demonstrated that significant changes in the circulating level of non-classical autoantibodies directed against G protein coupled receptors (GPCRs) of the autonomic nervous system also occur in patients

with SBI-associated FM (72). Anti-GPCR antibodies include antibodies to the adrenergic receptors (a1, a2, B1, B2), to muscarinic receptors (M1–M5), to the endothelin receptor A and to angiotensin II type1 receptor. These antibodies (agonists or antagonists) are involved in different physiological processes and pathological conditions (73-77). It has been postulated that dysregulation in the level and function of these anti-GPCRs autoantibodies are the cause for dysautonomia as observed in SBI-associated FM. Indeed, in animal models these autoantibodies have been demonstrated to cause symptoms as tachycardia, postural hypotension, decreased saliva production, and/or an overactive bladder (78, 79). These anti-GPCR antibodies can explain symptoms such as fatigue, muscle pain, cognitive impairment and/or irritable bowel syndrome (80, 81).

Coherence of evidence

Coherence is related to biological plausibility. It involves a coherent set of findings both from animal and human studies. Indeed, there is both human and animal evidence with regard to SBI causing dysautonomia symptoms (17, 82).

Experimental evidence

In animal models it has been demonstrated that in predisposed animals silicone gel and/or silicone implants may exacerbate autoimmune diseases (11, 12). In 1995, Naim *et al*. used Dark Agouti (DA) rats to study the arthritogenic potential of silicone gel and oil. DA rats have been shown to have a high susceptibility to develop arthritis. When bovine collagen II is injected together with incomplete Freund's adjuvant, these rats develop anti-collagen antibodies, a DTH reaction and arthritis. When bovine collage II is injected without the adjuvant, arthritis is not induced. However, when bovine collagen II was injected together with silicone gel (which was taken from McGhan SBIs) arthritis could be induced in these DA rats. Yet, silicone gel injection without bovine collagen II did not induce arthritis (11). Subsequently, Schaefer *et al*. used DBA/1 mice (a mouse strain in which arthritis occurs spontaneously at a low frequency and after immunisation with collagen in incomplete Freund's adjuvant (IFA) in 30% of the animals) to study the effect of breast implantation (McGhan SBI) or sham implantation on the occurrence of arthritis. The DBA/1 mice did get breast implants and after nine months the immunisation with collagen and IFA was performed. At 12 months, 90% of the mice developed arthritis, significantly more often than the sham implanted control mice. Disease severity was modestly but not significantly more severe in the mice with breast implants (83). In another set of experiments McDonald *et al*. studied the influence of injecting silicone gel from a sterile breast implant (Dow Corning) in NZB and BALB/c mice (12). Whereas BALB/c mice are not prone to spontaneous development of autoimmune diseases, NZB mic are used as a model for the spontaneous development of murine SLE. Silicone gel injections did not induce lupus nephritis in BALB/c mice, but the occurrence of lupus nephritis in NZB mice occurred earlier and was more severe in mice that received silicone gel injections. In addition, NZB mice developed more severe (haemolytic) anaemia after silicone gel injections (12). These experimental models demonstrate that SBI may exacerbate autoimmune diseases in patients that are (genetically) predisposed to these diseases but not in patients with a different genetic make-up.

So, in humans and in experimental models predisposed individuals may develop autoimmune diseases after SBI. But are there also experimental models to suggest that SBI may result in fibromyalgia or dysautonomia?

As mentioned previously, patients with SBI-associated FM have significant changes in the circulating level of anti-GPCR autoantibodies. Recently, Talalai *et al*. demonstrated that systemic symptoms of dysautonomia occur after intracerebroventricular injection of purified IgGs from SBI-associated FM patients into the CSF of mice (82), suggesting a direct pathogenic transferability of these autoantibodies. In these studies, male mice were subjected to intracerebroventricular (ICV) injection of a pool of IgG from patients with breast implants who experienced severe fatigue, widespread pain, and brain fog. A pool of IgG derived from healthy women was used as control. After ICV injection, the SBI IgG injected mice were immobile compared to naïve (not injected) mice and control IgG injected mice as tested in the open field test. No significant differences, however, were observed regarding the novel object location test and/or the forced swim test. Overall, the authors conclude that passive transfer of IgGs from symptomatic SBI women into mice brain affects locomotor activity and induces an animal apathetic behaviour (82). Although clearly more studies are needed to proof the pathogenic potential of IgG from SBI-associated FM women, these studies suggest that serum factors from SBI-associated FM patients may cause dysautonomia-related symptoms. The observations of Talalai *et al*. are corroborated by findings that recapitulate symptoms of dysautonomia with the use of other adjuvants in animal models (*e.g*., aluminum hydroxide) (84).

Recently, another animal model of breast implant illness was reported. Khan *et al*. demonstrated that patients with BII and fatigue, or myalgia, joint pain, or brain fog had higher oxylipin levels in the breast adipose tissue when compared to patients with breast implants but no BII and/or patients without breast implants (85). One of these oxylipins, oxylipin (E)-10-hydroxy-8-octadecenoic acid (10-HOME), correlated with the number of bacteria, *e.g*., Staphylococcus epidermidis, as observed in the biofilm around the implant and was found to be immunogenically capable of polarising naive CD4+ T cells with a resulting Th1 subtype. Importantly, when 10-HOME was injected into the abdominal mammary fat pad of mice, an increase of CD4+Th1 cells was found in the circulation of these mice, whereas the mice demonstrated BII- like symptoms (86).

Finally, explantation of the SBI (or "dechallenge") creates a "human experimental model" where the only contributing variable is removed and

all other, possibly relevant, factors remain the same for a given individual (with the same genetic and epigenetic variables). It is not yet clear why explantation results in amelioration of symptoms in SBI-associated FM. Previously, we postulated that explantation may either result in a reduction of the immune response or in a reduction of nociceptive signals (55). In this latter hypothesis, the breast implants may have acted as a physical and/or a psychological stressor.

Analogy: other examples of foreign body implants promoting dysautonomia

Silicone breast implants are the prototype of implant related dysautonomia. There is an abundance of published literature and medical experience spanning over 60 years supporting a causal link between the implants and dysautonomia symptoms in genetically predisposed individuals (31). It has been recently demonstrated that also other implants such as arthroplasty, polypropylene mesh, tension free vaginal tape, Essure devices, and/or metallic alloys as used in orthopaedic surgery can cause the same dysautonomia symptoms and that these symptoms disappear when the implant is removed (27, 87-90).

Conclusions

During the last decade it has been convincingly demonstrated that breast implants can trigger FM. Since patients with SBI-associated FM can be treated with explantation of the implants, resulting in improvement of their symptoms, we propose that patients with SBI-associated FM should be differentiated from patients with "idiopathic" FM. Furthermore, we propose that the causal link between breast implants and dysautonomia as observed in SBI-associated FM should be embraced by the various stake holders within the scientific community. This is of critical importance as there is clear (and preventable) harm that has resulted from a lack of consensus within the scientific community. We acknowledge that scientific consensus sometimes develops slowly on issues such as medical causation as has been clearly demonstrated with the long-lasting debate regarding the causal link between smoking and lung cancer (54).

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