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Review

Autoinflammatory/autoimmunity syndrome induced by adjuvants (ASIA; Shoenfeld's syndrome): A new flame

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ABSTRACT

In the present review, recent findings regarding autoimmune/inflammatory syndrome by adjuvants (ASIA) are described. Patients with ASIA present with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth. During the last few years, it has been postulated that these symptoms in patients with foreign body implants are due to a chronic inflammatory process and an adjuvant effect of the implanted biomaterial. Ultimately, these inflammatory reactions result in (an increase of) allergies, autoimmune diseases, immune deficiency and/or lymphomas.

Pre-existent allergic disease has been found to be an important risk factor for the development of ASIA after foreign body implantation. Explantation of the foreign body results in the majority of patients in an amelioration of the symptoms. There is an urgent need to start adequately adjusted epidemiological studies to obtain better evidence which percentage of patients does develop symptoms and/or diseases such as ASIA, immune deficiency, and/or autoimmune diseases after implant surgery.

Medical science puts great effort into elucidating the basis of inflammatory diseases; however, the mechanisms driving aberrant immune responses are mostly unknown and deserve further study.

A genetic predisposition has been found to play a pivotal role in the development of autoimmunity. In addition, it has become clear that various environmental factors may trigger these diseases in genetically predisposed individuals and that no single factor has been identified as prominent.

Importantly, during the last decade it has been recognized that autoinflammation ("Horror Autoinflammaticus"), immunodeficiency, and autoimmunity ("Horror Autotoxicus") represent axes of the multidimensional phenotype that may dictate the outcome of the complex interplay between genetic predisposition, environmental factors and immune dysregulation [1,2]. Both autoinflammatory and autoimmune disorders are characterized by aberrant changes in innate and adaptive immunity that may result in organ specific damage. Autoimmunity occurs upon a failure of the immune system to recognize the self-environment, whereas autoinflammatory diseases are driven by abnormal innate immune activation resulting for instance in activation of the inflammasome [1,3].

Few years ago, a syndrome entitled ASIA (Autoimmune/autoinflammatory syndrome induced by adjuvants; "Shoenfeld's syndrome") has been described and includes these diverse immune-mediated conditions all triggered by the exposure to an adjuvant [4,5]. Adjuvants are compounds that enhance a specific immune reaction resulting in higher titers of antibodies for instance against specific pathogens [6]. Well-known examples of adjuvants are aluminium hydroxide, squalene, and silica [7].

During the last decade, it became clear that also implanted foreign body materials such as silicones may act as an adjuvant [8,9]. Immediately after implantation of a biomaterial, a layer of host proteins is deposited onto the biomaterial surface resulting in the attraction of phagocytes (predominantly macrophages of the pro-inflammatory M1 subtype) [10]. Importantly, this process is critically dependent on the presence of activated mast cells and histamine [11]. Furthermore, biomaterials may act as an adjuvant resulting in the enhancement of the adaptive immune response to an auto-antigen [9]. Also, after implantation a biofilm is formed [12,13] and the micro-organisms in this biofilm may also act as adjuvants.

These effects are best studied in patients with silicone breast implants (SBI) [8].

Silicones are used in a variety of medical applications such as breast implants, hydrocephalus shunts, catheter lines, intra-ocular implants, rhinoplasty, hearing aids, laryngotracheal stenosis and various other stents, joint implants, testicular prosthesis and others. Silicones were introduced in the 60s and were thought to be biologically inert.

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Table 1
Criteria for the diagnosis of autoimmune/inflammatory syndrome induced by adjuvants (ASIA).

Major criteria
- Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestations
- The appearance of 'typical' clinical manifestations
  - Myalgia, Myositis or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, un-refreshing sleep or sleep disturbances
  - Neurological manifestations (especially associated with demyelination)
  - Cognitive impairment, memory loss
  - Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor criteria
- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syndrome)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease (i.e. multiple sclerosis, systemic sclerosis)

Patients are considered to have ASIA when either two major or one major and two minor criteria are present.

However, during the last 50 years it became clear that silicones induce various immunological effects. Not only silicones have adjuvant effects but also other materials that are used in humans such as polypropylene mesh used for hernia repair of abdominal wall defects [14], transvaginal implanted PP mesh used to reinforce a weak pelvic floor [14], urethral mesh slings such as tension-free vaginal tape (TVT) to treat female stress urinary incontinence [14], mineral oils and other materials that are used as cosmetic fillers [15], and prosthetic materials used for arthroplasty [16–18].

1. Clinical manifestations of ASIA

Typically, patients with ASIA present with chronic fatigue (Table 1). Patients are already tired when they wake up, whereas the fatigue is not alleviated by rest. Patients have a substantial reduction in the ability to engage pre-illness levels of occupational, educational, social and/or personal activities. Importantly, most patients report post-exertional malaise, also referred to as a symptom flare or "crash", which occurs following physical or cognitive exertion and can last from days to weeks. Sleep disturbances such as problems falling asleep and/or staying asleep are often present. Poor sleep quality is linked to greater fatigue. Probably also related to poor sleep quality are the symptoms of cognitive impairment resulting in memory deficits ("Alzheimer-light"), absent-mindedness, word-finding difficulties and difficulty paying attention.

Another early symptom is the occurrence of arthralgias or arthritis which is present in > 90% of the patients. Most patients fulfill the 2016 critera for fibromyalgia (see Table 2) [19]. Patients suffer from morning stiffness which sometimes may last more than an hour. Occasionally, however, patients present with a (symmetric) polyarthritis compatible with a diagnosis of rheumatoid arthritis [8].

In addition, up to 90% of the patients have myalgias and/or muscle weakness. Weakness can be severe and may render the patient to be bedridden. An EMG is frequently abnormal showing a "myopathic" pattern [8].

Furthermore, a majority of the patients report pyrexia whereas night sweats are common. Importantly, 75% of patients have dry eyes and/or a dry mouth. Symptoms of the dry eyes are often severe and may result in blurred vision and/or a keratitis sicca if left untreated. SSA/SSB antibodies are only present in a minority of patients [8], whereas salivary gland biopsies disclose mononuclear cell infiltrates different from what can be found in Sjogren's syndrome [8,20].

30–50% of the patients develop new-onset Raynaud's phenomenon sometimes with nailfold abnormalities suggestive of systemic sclerosis as demonstrated by capillaroscopy [8]

Table 2
Fibromyalgia 2016 criteria.

Criteria
A patient satisfies modified 2016 fibromyalgia criteria if the following 3 conditions are met:
(1) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9
(2) Generalized pain, defined as pain in at least 4 of 5 regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition
(3) Symptoms must have been present for at least 3 months
(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses

Notes
(1) WPI: note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.
(2) Symptom severity scale (SSS) score.
Fatigue
Waking unrefreshed.
Cognitive symptoms.
For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:
0 = No problem.
1 = Slight or mild problems, generally mild or intermittent.
2 = Moderate, considerable problems, often present and/or at a moderate level.
3 = Severe: pervasive, continuous, life-disturbing problems.
The symptom severity scale (SSS) score: is the sum of the severity scores of the 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) (0–9) plus the sum (0–3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:
(1) Headaches (0–1)
(2) Pain or cramps in lower abdomen (0–1)
(3) Depression (0–1)
The final symptom severity score (SSS) is between 0 and 12

Another important manifestation that is present in 30–40% of patients is the occurrence of severe neurological manifestations such as ischemic cerebral disease, a multiple sclerosis-like syndrome or a amyotrophic lateral sclerosis-like disease [8]. In patients with ischemic cerebral disease, anti-cardiolipin antibodies and/or lupus anticoagulant are detected in only a minority of the patients, whereas traditional risk factors for a CVA are often lacking as well.

Allergies are reported in 50–80% of the patients [14,21]. In most patients, these allergies are pre-existent. In many cases, however, the patient report that allergic complaints had disappeared before the SBI operation and returned thereafter. Allergic complaints include sneezing, itching of the nose and eyes, red eyes, rhinorrhea, nasal congestion and post nasal drip. Furthermore, asthmatic patients may suffer from cough, wheeze and shortness of breath. Food allergies also occur and about 10–20% of the patient develop new-onset urticarial and/or Quincke's edema. A remarkable frequent finding (about 50% of patients) is metal-allergy with nickel-induced dermatitis. Furthermore, some patients present with episodic symptoms suggesting a diagnosis of mast cell activation syndrome [8,22]. Finally, some patients present with a multiple chemical sensitivity syndrome [23].

Dyspnea in ASIA patients can be a result of severe asthma, pulmonary nodules, interstitial lung disease and/or pulmonary silicone embolism. Furthermore, 20–40% of patients suffer from severe and/or recurrent (upper respiratory tract) infections.

Cardiovascular complaints include signs of orthostatic intolerance such as dizziness, disturbed balance, irregular heartbeat and sometimes chest pain. A diagnosis of postural orthostatic tachycardia syndrome (POTS) is in patients with these symptoms frequently made. A mitral valve prolapse and/or joint hypermobility is found in about half of the patients [24].

Many patients suffer from gastrointestinal symptoms such as abdominal pain with changes in bowel movement patterns such as found in irritable bowel syndrome. Swallowing difficulties and/or dysphagia are in most cases related to the sicca complaints.

A substantial amount of patients (10–20%) have interstitial cystitis.

These patients suffer from chronic pain localized to the pelvic organs, pelvic floor myofascial support, or external genitalia often accompanied by urinary symptoms, such as urgency or frequency.

The skin may be painful and burning sensations ("pins and needles") suggest that (atypical) small fiber neuropathy is present [25].

At physical examination enlarged and tender lymph nodes (axillary, cervical and inguinal) are often found. A prominent livedo reticularis can be found in about 20–30% of patients, whereas mild livedo reticularis is present in another 30–40% of patients. Occasionally, tender subcutaneous nodules can be observed in the arms, legs, abdominal wall and/or elsewhere in the body. Histologically, these nodules demonstrate granulomatous inflammation (e.g., migratory silicone granulomas) [8]. Finally, 20–40% of patients have ill-defined skin rashes, unexplained (sometimes severe) pruritus and/or alopecia.

2. Diagnostic procedures in ASIA

Laboratory evaluations are often non-specific.

Generally, CRP levels are normal. Angiotensin converting enzyme and soluble interleukin-2 receptor levels are, however, in up to 50% of patients elevated.

In ASIA, either induced by vaccines or by foreign body implantation, autoimmunity may be induced [8,26–30]. So, a broad spectrum of autoantibodies should be tested. Antinuclear antibodies are present in 20% of patients, whereas various other antibodies such as anti-SSA/SSB, anti-dsDNA, anti-Scl-70, anti-cardiolipin, anti-CCP antibodies, IgM-rheumatoid factor, cryoglobulins, and/or ANCA (i.e., proteinase 3-ANCA, myeloperoxidase-ANCA and/or ANCA with other specificities) may be found as well [8,14]. Vitamin D insufficiency and/or deficiency is a frequent finding and 20–50% of patients have decreased levels of IgG and/or IgG subclasses [8,14,26–28].

There are several diagnostic procedures to objectify the complaints of the patients. These other procedures are, however, non-specific.

Examples are a cardiopulomonary exercise test by cycling till maximal exertion that is repeated after 24 h to objectify the post-exertional malaise [31], overnight polysomnography to ascertain objectively poor sleep quality, capillaroscopy to detect nailfold abnormalities, a skin biopsy showing reduced intraepidermal nerve fiber density and/or abnormal temperature threshold testing to confirm small fiber neuropathy [25], and/or ocular surface evaluation including Schirmer testing, tear breakup time, and staining of the cornea and conjunctiva to confirm the impaired tear production. Furthermore, histological examinations of explanted implants and/or lymph nodes may confirm granulomatous inflammation. Labial salivary gland biopsies may confirm mild lymphocytic infiltration differentiating sicca symptoms in ASIA patients from patients with Sjogren's syndrome [20].

2.1. Case report

A 40 year old woman visited my Autoimmunity Clinic in December 2016 with recurrent fever. Fevers started 5 years before presentation. At that time, the patient also developed alopecia areata and weight loss. For these recurrent fevers, she had been several times hospitalized in both teaching hospitals and a university hospital. A diagnosis could not be made. Two years before presentation, a late seroma of the right breast and a subcutaneous nodule on her left leg developed. A biopsy of both the subcutaneous nodule and a punction of the seroma disclosed non-specific inflammation. At presentation at my Clinic, she reported that she experienced since 5 years severe fatigue with post exertional malaise, widespread pain, myalgias, arthralgias, dry eyes/dry mouth with gum disease, Raynaud's phenomenon and problems with concentration. Furthermore, she reported to have allergies for pollen, house dust, cats, dogs and nickel that started already during childhood.

The patient's history revealed that she had silicone breast implants (SBI) placed in 2006 because of cosmetic reasons. These implants caused severe capsule formation (Baker grade IV) and were replaced by new SBI in 2010.

At physical examination, multiple tender cervical, axillary, and inguinal lymph nodes were present. Examination of the joints reveled a trigger point score of 16/18. The right breast was firm and tender, whereas the left breast was supple.

Laboratory tests revealed no abnormalities apart from an elevated IgE (205 IU) and a decreased level of 25-OH cholecalciferol (32 ng/ml). Tests for a M-protein, ANA, ANCA, anti-CCP and rheumatoid factor were all negative. Anti-SSA testing revealed a positive anti-Ro-60 but a negative anti-Ro-52.

A diagnosis of ASIA due to silicone implant incompatibility syndrome was made and because of a strong clinical suspicion of Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) explantation of the breast implants was arranged.

3. Silicone breast complications

3.1. ASIA, autoimmune diseases, immune deficiency and BIA-ALCL

After SBI, local and distant complications of the SBI procedure are being reported. Local complications of SBI are pain, swelling, redness, infections, capsular contracture, and/or implant rupture. As a result, changes in breast shape, breast asymmetry, firmness of the breasts and breast enlargement may be noticed. Furthermore, general complications occur. Patients present with arthralgias, fatigue, and other symptoms of ASIA (Table 1), immune deficiency, autoinflammatory and/or auto-immune diseases [8]. These symptoms received during the last 50 years several different names: human adjuvant disease, siliconosis, silicone implant incompatibility syndrome, silicone-induced toxicity and –more recently- autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [5,8,26,28]. Both patients and doctors suspect that these complaints are caused by the implants. Indeed, removal of the SBI results in an amelioration of symptoms in 60–80% of the patients [32]. It is currently postulated that SBI cause an inflammatory reaction and that silicon-containing particles are transported to regional lymph nodes, resulting in a pronounced adjuvant effect [8].

In 2013, we reported 32 patients with ASIA due to silicone incompatibility syndrome [28]. Median time between start of complaints and time of breast implant was 10 years (2–24 years). 53% of the ASIA patients had an established systemic autoimmune disease, 22% of patients had an organ-specific autoimmune disease and 47% of patients a humoral immunodeficiency (either hypogammaglobulinemia or a IgG subclass deficiency). Subsequently, many patients with self-reported symptoms were evaluated in the Netherlands [21,26]. From these, about 95% fulfilled the criteria for ASIA.

At present, there are no epidemiologic studies performed to calculate the risk of ASIA in SBI patients. In a small study, we evaluated symptoms in consecutive patients with SBI and found that ASIA symptoms occurred 3 x more often compared to age- and sex-matched controls without breast implants. Clearly, more epidemiological studies on the association between ASIA and SBI are needed.

Many patients with silicone-related disease fulfill the criteria for CFS/ME [33], fibromyalgia [19], undifferentiated connective tissue disease [34] and/or sarcoid-like disease [8,35]. Sarcoid-like disease is due to infiltration of silicones in lymph nodes, lungs and various other tissues. Histopathologically findings are, however, very difficult to differentiate from "idiopathic" sarcoidosis.

Furthermore, a substantial number of patients have well-defined other systemic auto-immune diseases such as Sjogren syndrome, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome, eosinophilic granulomatosis with polyangiitis and different other forms of vasculitis [8,26,36–38]. Epidemiologic evidence for an increased occurrence of these autoimmune diseases is, however, sparse [39]. In a meta-analysis published in 2016, an increased risk for rheumatoid arthritis and Sjögren syndrome was found. Importantly, it was concluded that studies still do not provide

conclusive evidence regarding safety of SBI [39]. Recently, Watad et al. reported a large epidemiological study from Israel [40]. 24.651 SBI patients were compared with 98.604 matched controls without a breast implant. An increased risk for the development of autoimmune diseases was found (OR 1.21, 95% CI 1.17–1.26). The strongest associations were found with sarcoidosis, Sjogren's syndrome and systemic sclerosis (SSc) [40]. Recently, we collected data from all SSc patients included in the Leiden Systemic Sclerosis Cohort. Between April 2009 and January 2014. In 278 females with SSc, nine patients had SBIs (mean age, 57 years; range, 22–69 years). In 8 patients the SBIs were placed before the development of SSc, the time since SBIs and development of SSc being 16 years (range, 1–40 years) [38].

Local complications may be due to ruptures and/or gel bleeding through an intact capsule, resulting in capsular contractures, silicone-induced granuloma of the breast and/or BIA-ALCL. Furthermore, many patients develop silicone-containing granulomas in lymph nodes as detected by ultrasonographic examination showing a typical “snow-storm sign” [41].

SBI patients clearly have an increased risk to develop lymphomas [42–45]. Especially, 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. Typical presenting symptoms of ALCL include a late-onset periprosthetic seroma and/or swelling of the breast months to years after the surgical incision has healed. In a recent study from the Netherlands, ALCL in the breast was diagnosed in 47 patients during a period from 1990 to 2016. 32 of these 47 patients were breast implant exposed cases (OR in SBI patients: 421.8; 95% CI 52.6–3385.2) [45]. De Boer et al. calculated that 1 in 6920 SBI patients will develop BIA-ALCL before the age of 75 years. BIA-ALCL occurs mainly in silicone-filled breast implants. Moreover, the risk to develop BIA-ALCL is increased when macro-textured breast implants are used compared to micro-textured implants [45].

4. Pathophysiology of SBI related complications

In general, commonly used biomaterials for implantation are non-immunogenic and non-toxic. Despite this, implanted biomaterials trigger a foreign body reaction resulting in granulomatous inflammation [10,46]. Furthermore, microbial biofilms form on implants [12,13] contributing to the chronic inflammatory response. Importantly, implanted biomaterials act as an adjuvant in the enhancement of an immune response to an antigen [9].

Furthermore, in women with SBI it is found that the capsule around these SBIs contain inflammatory cells that are predominantly Th1/Th17 cells, whereas regulatory T cells in the capsules are defective in suppressing these intracapsular T cells [47]. These findings suggest that the Th17/Treg balance is disturbed which may result in the development of inflammatory/autoimmune diseases [48].

Silicone-gel may migrate outside the outer shell after SBI rupture. Migration through an intact shell, however, has also been demonstrated (so-called “gel bleed”). Recently, silicone material was found in multiple organs, nervous tissue and the brain at autopsy in a patient that had been exposed during a period of 17 years to gel bleed from her silicone breast implants [49].

The association between SBI and ASIA may result in the following scenario [8,50–52]: Silicon-containing particles are captured by macrophages, resulting in entrapment within lysosomes. Subsequently, inflammasomes are activated, resulting in the production of cytokines such as interleukin-1β. Also, reactive oxygen species (ROS) and reactive nitrogen species are produced. Subsequently, apoptosis of macrophages occurs resulting in the release of silicon-containing particles that can be taken up once again by other macrophages. Exposure to silicon-containing particles also leads to a massive production of interleukin-17 resulting in an influx of neutrophils that are activated and produce ROS and release enzymes such as myeloperoxidase. Additionally, silicon-containing particles are transported to the regional lymph nodes, resulting in a pronounced adjuvant effect.

In animal models, it has been shown that SBI induces an adjuvant effect [53–55] and increase the susceptibility to and/or exacerbate auto-immune diseases [56–58]. In non-susceptible animals, however, autoimmunity could not be induced [56].

At present it is unknown which women are susceptible for development of SBI related disease. Several factors, however, have been postulated [59].

Importantly, patients who are known to have (a history of) allergy are at risk to develop ASIA after SBI [21] or after a mesh implantation [14]. Furthermore, patients with an established autoimmune disease or a familial predisposition for auto-immune disease are at risk to develop symptoms after SBI. It is important to realize that not only immunogenetic (i.e., HLA) factors play a role in the development of SBI induced ASIA but probably also environmental factors such as smoking and obesity [27,37,60].

Importantly, many patients with ASIA have a humoral immune-deficiency [14,26,28] and/or a vitamin D deficiency [27]. These two factors also increase the risk to develop an autoimmune disease in susceptible patients [8]. Furthermore, the chronic SBI-induced inflammation in the capsule with its biofilm may result in progression from a polyclonal lymphocyte stimulation to a monoclonal lymphocyte stimulation, which in turn will result in lymphoma formation such as ALCL [43,61].

5. Case report (continued)

During explantation, the right SBI appeared to be ruptured. Furthermore, a large capsule was found around the prosthesis. Histological examination (performed by Professor Daphne de Jong, Free University, Amsterdam, the Netherlands) revealed a dense lymphoid infiltrate with many plasma cells that showed Russell bodies, eosinophils, histiocytes and giant cells. Several large atypical cells were present as well. Immunohistochemistry revealed CD30 positive plasma cells and an extensive T cell infiltrate. T cells were negative for CD30, positive for CD3, CD5, CD2, and CD7 without loss of immunohistological markers. A diagnosis of silicone-induced granuloma of breast implant [62] was made without signs of a lymphoma.

Post-operative the patient experienced fever, weight loss, and an increase of malaise, arthralgias and myalgias. She was treated with prednisone (start dose 20 mg) in combination with maintenance therapy with doxycycline (100 mg/day) with a good recovery.

6. Disease management of ASIA

Unfortunately, there are no randomized clinical trials performed regarding the management of ASIA. Also, there are no (inter)national guidelines formulated. However, based on our personal experience some therapeutic considerations can be made [63].

Firstly, vitamin D deficiency and/or insufficiency should be corrected. Since vitamin D may act as a regulatory agent of the immune system [64,65], we prescribe vitamin D supplementation to our patients [65,66]. Importantly, vitamin D also has been demonstrated to decrease chronic widespread pain and/or fatigue [67,68].

Secondly, triggers of immune activation should be avoided and/or treated. The patient should try to quit smoking. Furthermore, anti-allergic medication should be prescribed to patients with allergic rhino-sinusitis whereas bacterial (respiratory) infections should be treated with antibiotics, especially when IgG levels and/or IgG subclasses are deficient [69].

There is evidence that explantation of a SBI and/or a polypropylene mesh is an important first step in the management of patients with ASIA due to an implant [8,14,26,32]. Unfortunately, several women still suffer from ASIA after explantation. There are no medications that can cure ASIA, but therapy can help reduce symptoms. Suggested

medications include minocycline or doxycycline [70–72], hydroxychloroquine or corticosteroids to dampen inflammation. In severe cases, 2 mg/kg IVIg may be used. In addition, medication may be prescribed for symptoms due to central sensitization, dry mouth/dry eyes, gastrointestinal involvement and/or cardiovascular involvement (reviewed in 63). Finally, as in patients with fibromyalgia a combination of drug, cognitive behavioral and exercise treatment should be considered, whereas some patients need psychiatric consultation [63].

7. Conclusion

ASIA presents with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth. During the last few years, it has been postulated that these symptoms in patients with foreign body implants are due to a chronic inflammatory process and an adjuvant effect of the implanted biomaterial. Ultimately, these inflammatory reactions result in (an increase of) allergies, autoimmune diseases, immune deficiency and/or lymphomas.

Pre-existent allergic disease has been found to be an important risk factor for the development of ASIA after foreign body implantation. Explantation of the foreign body results in the majority of patients in an amelioration of the symptoms. There is an urgent need to start adequately adjusted epidemiological studies to obtain better evidence which percentage of patients does develop symptoms and/or diseases such as ASIA, immune deficiency, and/or autoimmune diseases after implant surgery.

Therefore, I postulate that ASIA is a new flame -just as Simply Red song in 1989

She's turned me round
A new flame has come
And nothing she can do
Can do me wrong

Alternatively, we can –at least- simply conclude that “a new disease is defined” …

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