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SPECIAL ARTICLE

Women with silicone breast implants and unexplained systemic symptoms: a descriptive cohort study

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ABSTRACT

Background: Since their introduction, the safety of silicone breast implants has been under debate. Although an association with systemic diseases was never established, women continuously blamed implants for their unexplained systemic symptoms. In 2011, a pattern of symptoms caused by systemic reactions to adjuvants (e.g. vaccines, silicone) was identified: 'autoimmune syndrome induced by adjuvants' (ASIA). Our aim was to collect a cohort of women with silicone breast implants and unexplained systemic symptoms to identify a possible pattern and compare this with ASIA.

Methods: Women with silicone breast implants and unexplained systemic symptoms were invited through national media to visit a special outpatient clinic in Amsterdam. All were examined by experienced consultant physicians and interviewed. Chest X-ray and laboratory tests were performed.

Results: Between March 2012 and 2013, 80 women were included, of which 75% reported pre-existent allergies. After a symptom-free period of years, a pattern of systemic symptoms developed, which included fatigue, neurasthenia, myalgia, arthralgia and morning stiffness in more than 65% of women. All had at least two major ASIA criteria and 79% fulfilled ≥3 typical clinical ASIA manifestations. After explantation, 36 out of 52 women experienced a significant reduction of symptoms.

Conclusions: After excluding alternative explanations, a clear pattern of signs and symptoms was recognised. Most women had pre-existent allergies, suggesting that intolerance to silicone or other substances in the implants might cause their symptoms. In 69% of women, explantation of implants reduced symptoms. Therefore, physicians should recognise this pattern and consider referring patients for explantation.

KEYWORDS

Allergy, autoimmune induced adjuvant disease (ASIA), explantation; silicone breast implants, systemic symptoms

BACKGROUND

Since their introduction to the market in 1962, silicone breast implants have been the subject of international debate. From 1992 to 2006, the Food and Drug Administration (FDA) restricted the use of silicone breast implants due to controversy about their safety and concerns about their association with systemic symptoms and alleged autoimmune diseases.[1,2] Currently, over four million women worldwide have been augmented or reconstructed with silicone breast implants.[3] The vast majority of these women seem satisfied with their implants and do not experience any local or systemic symptoms.[4]

The question whether silicone breast implants can cause serious systemic health problems has often been posed but seldom thoroughly answered.[5] Local complications described are breast pain, capsular contraction, implant rupture, asymmetry, and infection.[6,7] In addition, breast implants have been associated with a very rare type of lymphoma.[8] Although often suggested,[9,10] no studies could confirm strong associations between silicone breast implants and atypical systemic symptoms or well-defined autoimmune diseases.[11,12]

Alternatively, some authors have reported a pattern of symptoms in patients with silicone breast implants that mimic autoimmune diseases.[10,13] In the early 1990s, this even led to the introduction of a new 'disease' called 'siliconosis' or 'silicone reactive disorder' with symptoms such as memory loss, fever, morning stiffness, paraesthesia, hair loss, sweating, and joint pain. These 'diseases' were

introduced by lawyers in lawsuits against breast implant manufacturers.[10,13] In 2004, a causal relationship between these symptoms and silicone breast implants was still not confirmed.[14] In 2011, immunologists, however, discovered similarities with systemic symptoms and immunological reactions to other adjuvants, such as vaccines. A syndrome called 'autoimmune (autoinflammatory) syndrome induced by adjuvants' (ASIA) was introduced and defined by several major and minor criteria (*table 1*).[15] According to two Dutch authors at least two major criteria or one major and two minor criteria are required for the diagnosis of ASIA.[16] Until now, only a few case series have reported women with silicone implants who fulfil the criteria of ASIA.[17,18]

The recent recall of silicone breast implants of the French manufacturer Poly Implant Prothèse (PIP), due to fraudulent usage of industrial silicone gel, has reignited the debate on the safety of silicone implants.[19,20] As a result, worried patients with implants from different manufacturers presented to their GPs, plastic surgeons, and other physicians with unexplained systemic symptoms. Most of these women felt ignored, as physicians tend to deny any association between silicone implants and their complaints. In addition, several of these women even went to court to get recognition for their health problems, which they believe to be caused by their silicone breast implants. Therefore, Dutch health authorities in association with the Netherlands Society of Internal Medicine and Netherlands Society of Plastic Surgery introduced a special outpatient clinic for women with silicone breast implants and unexplained systemic symptoms, which resulted in the present inventory.

Table 1. *Suggested criteria for diagnosis of ASIA*

MAJOR CRITERIA
1. Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
2. The appearance of 'typical' clinical manifestations:
• Myalgia, myositis or muscle weakness
• Arthralgia and/or arthritis
• Chronic fatigue, unrefreshing sleep or sleep disturbances
• Neurological manifestations (especially associated with demyelination)
• Cognitive impairment, memory loss
• Pyrexia, dry mouth
3. Removal of inciting agent induces improvement
4. Typical biopsy of involved organs
MINOR CRITERIA
1. The appearance of autoantibodies or antibodies directed at the suspected adjuvant
2. Other clinical manifestations (i.e. irritable bowel syndrome)
3. Specific HLA (i.e. HLA DRB1, HLA DQB1)
4. Evolvement of an autoimmune disease (i.e. MS, SSc)

ASIA = autoimmune (auto inflammatory) syndrome induced by adjuvants; HLA = human leukocyte antigen; MS = multiple sclerosis; SSc = systemic sclerosis.

The aim of this descriptive cohort study was to identify a possible pattern of symptoms in a cohort of women with silicone breast implants and unexplained systemic symptoms. In addition, similarities between these symptoms and the so-called ASIA syndrome were explored.

PATIENTS AND METHODS

In December 2011, Dutch women with silicone breast implants and systemic symptoms were invited by the national media (e.g. television and internet) to attend a specialised outpatient clinic at VU University Medical Center in Amsterdam. This descriptive cohort study was approved by the Medical Ethics Review Committee of the VU University Medical Center. All women visited the clinic on their own request and none were rejected for evaluation. Women with any type of silicone breast implants were accepted. At the outpatient clinic, medical history and physical examination were performed by an experienced internist to exclude any alternative explanation for the complaints.

A detailed medical history was taken with special attention to the characteristics of the implants (e.g. type of implant, reason for implantation) and experienced symptoms (e.g. time to symptoms, local complaints, and systemic symptoms). The physical examination consisted of a general examination with special attention for breast and axillary lymph nodes. All women underwent chest X-ray (to exclude sarcoidosis) and general laboratory blood tests, including C-reactive protein (CRP), haemoglobin, thrombocytes, leucocytes with differentiation, renal function and liver enzymes. On indication, with the aim of excluding alternative explanations for their complaints, additional imaging tests and immunological serology were performed (e.g. antinuclear factor (ANF)).

After the visit to the outpatient clinic, additional data were obtained using a structured questionnaire. To this end, all women were contacted by phone and interviewed by an independent researcher. According to the questionnaire, women were asked in detail about the implantation history and self-reported symptoms.

Finally, the collected data were analysed using SPSS software (SPSS for Windows 21.0, Inc., Chicago, IL, USA 2012). For the analysis, self-reported symptoms were compared with the ASIA criteria as mentioned in *table 1*. Data are presented as median with range.

RESULTS

From March 2012 to March 2013, 84 women and two men presented to the specialised outpatient clinic. Four out

of the 84 women declined participation in the inventory. In addition, two male patients with silicone testes were excluded from the cohort. Finally, 80 women with silicone breast implants and systemic symptoms could be included in the analysis. Characteristics of these 80 women are summarised in *table 2*. The median age was 47 years (range 22-78 years). The majority of women (89%) had silicone breast implants for cosmetic reasons. The median total exposure time to silicone breast implants was 14.5 years (range 2-42 years). Although most women did not have a medical history besides breast augmentation, 60 out of 80 women (75%) reported pre-existent allergy (*table 2*) prior to implantation.

Of the 80 included women, 79% of them had local symptoms such as breast pain or capsular contraction (*table 3*). Besides local symptoms, all women reported systemic symptoms (*table 4*). The most frequently reported symptoms included fatigue (89%), neurasthenia (74%), joint pain (69%), muscle pain (65%), morning stiffness (65%), night sweats (63%), and dyspnoea (45%). In addition, women experienced cognitive problems (35%), dermatological symptoms (31%), gastrointestinal symptoms (30%), and alopecia (23%). Of note, only a minority of women reported psychological symptoms including sleeping disorders (19%) and depression (4%). While being exposed to silicone breast implants, 11 out of 80 women (14%) developed a total of 14 confirmed autoimmune diseases at a median time of seven years after first implantation (range 3-30 years; *table 5*). In the women who were not diagnosed with an autoimmune disease, routine blood tests, chest X-ray, and additional investigations did not show significant abnormalities, with the exception that ANF serology was positive in 20% of the women.

Following implantation of silicone breast implants, the women reported a symptom-free period with a median of 4.5 years (range 1 month to 30 years). In most women, the symptoms developed gradually or semi-acutely, but in 11 out of 80 women the onset of all their complaints was quite acute. Shortly before the onset of their symptoms, two women had undergone a mammography, one woman had a closed capsulotomy, and another woman had experienced a trauma with a ball on the thorax.

When classified according to the suggested ASIA criteria (*table 1*), as summarised in *table 6*, all women had at least two major ASIA criteria and 79% of the women even fulfilled ≥3 typical clinical ASIA criteria manifestations. Besides memory loss, other cognitive impairments (*table 1*) were noticed such as word finding problems, coordination and concentration problems.

Because of the unexplained symptoms a number of women decided to have the implant explanted. At the time of the analysis, 52 out of 80 women had had an explantation of

Table 2. *Characteristics of 80 women with silicone breast implants and unexplained systemic symptoms*

	n	%
Age (years)		
<30	4	5
30-40	11	14
40-50	29	36
50-60	21	26
60-70	14	18
>70	1	1
Intoxications		
Nicotine	25	31
Alcohol	45	56
Other drugs	1	1
Known allergy		
None	20	25
Metals	3	4
Food	2	2
Atopic constitution*	19	24
Medicines	14	17
Latex/rubber/plasters	3	4
Multiple	19	24
Silicone exposure (years)		
<5	4	5
5-10	15	19
10-15	21	26
15-20	13	16
20-25	8	10
>25	19	24
Implant replacements		
None	35	44
1-2	31	39
3-5	13	16
>5	1	1
Reason for implantation		
Augmentation	71	89
Reconstruction	9	11

n = number of women; % = percentage of women; *eczema, hay fever, pollen and dust mites allergy.

Table 3. *Local symptoms in 80 women with silicone breast implants and unexplained systemic symptoms*

	n	%
None	17	21
Pain	41	51
Capsular contraction	40	50
Lymphadenopathy*	28	35
Changed size, form or consistence	20	25
Lost sensibility	9	11
Infection	5	6
Local skin disorders	3	4
Rotation	1	1

n = number of women affected; % = percentage of women affected *axillary (n= 16), neck (n = 10), thoracic wall (n= 2).

Table 4. *Pattern of unexplained systemic symptoms in 80 women with silicone breast implants*

	n	%
Fatigue	71	89
Neurasthenia of the extremities*	59	74
Arthralgia**	55	69
Myalgia	52	65
Morning stiffness***	52	65
Night sweats	50	63
Dyspnoea	36	45
Cognitive problems†	28	35
Dermatological symptoms‡	25	31
Disorders of digestive tract	24	30
Alopecia	18	23

n = number of women affected; % = percentage of women; *patients described pins and needles, tingling, feeling of numbness, a heavy feeling in the extremities; **mostly in the small joints of the hands and feet; ***severe stiffness for more than 30 minutes; †word finding problems, concentration and coordination problems and memory loss; ‡rash, eczema, urticaria and itch.

Table 5. *Confirmed autoimmune disease in 11 women with silicone breast implants and unexplained systemic symptoms*

Confirmed disease*	n
Antiphospholipid syndrome	1
Scleroderma	1
Systemic lupus erythematosus	1
Sjögren's disease	2
Ulcerative colitis	1
Crohn's disease	1
Psoriatic arthritis	2
Autoimmune hepatitis	1
Perniciosa	2
Lichen sclerosis	2

n = number of women; *some women have more than one confirmed diagnosis.

Table 6. *Eighty women with silicone breast implants and a pattern of unexplained systemic symptoms according to ASIA criteria*

	n	%
MAJOR CRITERIA OF ASIA		
1. Exposure to external stimuli	80	100
2. Typical clinical manifestations		
Chronic fatigue or sleep disturbances	72	90
Neurological manifestations (demyelination)*	59	74
Arthralgia and/or arthritis	55	69
Myalgia	52	65
Cognitive impairment, memory loss**	28	35
Pyrexia, dry mouth	25	31
3. Removal of stimuli leads to improvement		
Explantation or replacement not yet done	30	38
No improvement yet***	17	21
Significant improvement	33	41
4. Typical biopsy		
Pathology not done	62	77
Silicone in lymph node	3	4
Silicone found in capsular tissue	12	15
Histiocytic reaction	3	4
MINOR CRITERIA OF ASIA		
1. The appearance of autoantibodies: ANF serology		
Unknown	10	12
Weak positive	16	20
Doubtful	11	14
Negative	43	54
2. Other clinical manifestations†	.	.
3. Specific HLA (i.e. HLA DRB1, HLA DQB1) ‡	.	.
4. Evolvement of an autoimmune disease	11	14

ASIA = autoimmune (autoinflammatory) syndrome induced by adjuvants; n = number of women affected; % = percentage of women; *neurasthenia was included; **memory loss, word finding disorders, coordination and concentration problems; ***limited follow-up; ANF = antinuclear factor; †to the authors it remains unclear which manifestations can be included; HLA = human leukocyte antigen; ‡not done.

their breast implants. Currently, the median follow-up after explantation is seven months (range 1 month to 18 years). Among the 52 women who underwent explantation, 36 women reported a significant decrease of their symptoms, whereas nine of these 36 women stated that their symptoms had completely disappeared.

DISCUSSION

The present nationwide study shows a pattern of self-reported symptoms in 80 women with silicone breast implants and unexplained symptoms, which included fatigue, muscular and joint pain, morning stiffness, neurasthenia, pulmonary, cognitive and dermatological symptoms. The observed pattern of symptoms resembled the typical clinical manifestations of ASIA.[15] All women had at least two major criteria and 79% of them had more than three typical clinical manifestations. In addition, 79% of women had local symptoms such as breast pain or capsular contraction. Furthermore, 75% of women reported a history of allergy before implantation. Because of their unexplained symptoms, 52 women decided to explant the silicone implants and 36 of these women reported significant reduction of their symptoms.

In our population, we identified a clear pattern of self-reported symptoms, which resembled a newly introduced syndrome, known as ASIA. Although most studies could not confirm an association between silicone implants and connective tissues diseases,[11,21] a few studies demonstrated an association between implants and undefined symptoms such as fatigue, arthralgia, myalgia

and cognitive symptoms.[10,22,23] In the present cohort, most women reported semi-acute onset of their symptoms, which could be explained by implant rupture or silicone gel bleeding. Previously, it has been described that symptoms of chronic fatigue, impaired short-term memory and multi-joint pain can develop after implant rupture.[24]

Besides systemic symptoms, 79% of women experienced local symptoms such as breast pain or capsular contraction, suggesting an association between local and systemic symptoms in our population. In line with these clinical observations, associations between local breast symptoms and systemic symptoms as well as immune factors have been described earlier in women with silicone breast implants. For example, capsular contraction has been demonstrated to be associated with systemic symptoms and circulating immune complexes.[25,26] Women with silicone breast implants and autoimmune diseases have shown differences in human leukocyte antigen (HLA) typing as compared with asymptomatic women with implants.[27] HLA DR and HLA DQ positive haplotypes are overrepresented in women with silicone breast implants and systemic symptoms.[13] In a recent study, it has been demonstrated that in susceptible individuals a disturbance in the modulation of key cytokines might be responsible for a perpetuation of the inflammatory reaction, which locally causes capsular contracture and systemically may trigger autoimmune diseases.[28] When left in situ, capsular tissue may continue to provoke systemic symptoms even after explantation of the silicone implants.[29]

Prior to implantation, the majority of women (75%) reported a pre-existent allergy. Silicone is generally believed to be a biologically inert product and used in many medical devices including artificial valves, joints and needles.[30] However, recent case reports have described allergy-like reactions in patients with silicone in pacemakers, nasogastric tubes and cochlear implants.[31-33] More recently, Hajdu *et al.*[34] suggested that systemic symptoms following exposure to silicone, such as described in ASIA, may only appear in subjects with underlying diseases or high susceptibility. In addition, a study in 2008 demonstrated that women with silicone breast implants had a higher serum IgE than women without silicone breast implants.[35] The results of our study subscribe to the hypothesis that silicone or other chemical substances in the implants may cause systemic symptoms in women with atopy or a hyperimmune state.

After explantation of silicone implants, 36 out of 52 women experienced a significant reduction of their symptoms. In the literature, only a few studies have described the outcome of explantations in patients with silicone implants and unexplained systemic symptoms. In several studies, recovery of these symptoms has been described after explantation, but prospective studies are lacking.[36-38] Although the follow-up of the present cohort is too limited for definite conclusions, our findings suggest that explantation may be an adequate treatment for unexplained systemic symptoms in women with silicone breast implants. As capsular tissue can function as an adjuvant itself, capsulectomy should be considered as well. Although we noticed a significant improvement in many patients after explantation these results should be interpreted with caution because there was no control group. We will continue to include patients in this cohort in the future, with the aim of following them up for at least five years. We will start using a standardised questionnaire before and after explantation to gather information on systemic symptoms prospectively.

Another potential limitation of this study is the design, as women with silicone breast implants and unexplained symptoms visited the specialised clinic on their own request, leading to selection bias. In addition, as most of the signs and symptoms were subjective, recall bias or suggestion cannot be excluded. Although, it is worth mentioning that two experienced clinicians with vast experience examined these patients looking for alternative explanations for their symptoms, before including them in the present descriptive cohort study. Since radiology investigations were not performed routinely, due to financial limitations, it was not possible to investigate the relation between silicone leakage and unexplained symptoms. As the Netherlands is a relatively small country, enabling travelling from every region to our clinic, we expected a large number of women to visit the clinic. Although women came from all over the Netherlands, only 84 women visited the clinic within 12 months. As the women had easy access to the specialised clinic and their visits were paid by the Dutch insurance companies, we believe that a representative number of women visited this clinic. As a result, we may conclude that the prevalence of unexplained systemic symptoms in women with silicone breast implants is probably low.

Although questioned for decades, the safety of these implants has not been adequately investigated. Since the PIP debacle, the importance of large prospective registration studies and post-market surveillance for medical devices has been frequently emphasised.[39,40] As long as such studies are lacking, observational and retrospective studies may provide valuable information. We realise that the present study has several limitations, but believe that our preliminary findings may help physicians, such as general practitioners, plastic surgeons and internists, to recognise this pattern of systemic symptoms in women with silicone breast implants and unexplained symptoms. Although the prevalence of this pattern appears to be low it is of significant importance to recognise these symptoms and consider explantation as the unexplained symptoms may lead to unnecessary health care consumption in women with silicone breast implants.

CONCLUSIONS

In the present descriptive cohort study in the Netherlands, the unexplained systemic symptoms in 80 women with silicone breast implants were evaluated. A clear pattern of symptoms was reported including fatigue, joint and muscle pain, morning stiffness, night sweats, cognitive and dermatological complaints. The observed pattern of symptoms was compatible with ASIA. Most women (75%) with silicone breast implants and unexplained systemic symptoms had pre-existent allergies, suggesting that intolerance to silicone or other substances in the implants might cause these symptoms. In these susceptible women, explantation of the implants may reduce the symptoms. Although the prevalence of this pattern appears to be low, it is of significant importance to recognise these symptoms and consider explantation of the silicone implants and capsulectomy. Therefore, this article's primary message is to recognise and treat this pattern in susceptible women with silicone breast implants. Especially, when the alternative explanations are unavailable, the probable association between the silicone implants and their complaints should be taken seriously.

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