'Angry back syndrome': a non-reproducible phenomenon

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Summary

The term 'angry back syndrome' (ABS) was coined by Mitchell in 1975. It was stated that a strong positive patch test reaction could create an 'angry back' which becomes hyper-reactive to other patch test challenges. The present study investigated whether the ABS is a generalized state of hyper-reactivity of skin, whether it is a localized hyper-reactivity of skin, i.e. only in the close proximity to a strong patch test reaction, whether it is an individual specific phenomenon and if ABS is a reproducible phenomenon. The studies failed to demonstrate any generalized or localized change in the reactivity of the skin. This left the possibility that ABS might be a rare, and individual-specific phenomenon. However, even in the subjects who had previously been diagnosed as having ABS we failed to reproduce the angry back.

Angry back syndrome (ABS) is a term invented by Mitchell in a paper with many bold statements, although without any supporting data. Mitchell stated that a strong positive patch test reaction creates an angry back, which become hyper-reactive to other patch test challenges. Furthermore, he maintained that if one strong positive patch test reaction is obtained, no credence could be given to any concomitant positive reactions. In another paper Mitchell reported 55 patients who showed 30 two plus (2+) and 90 one plus (1+) patch test reactions. When these subjects were re-tested with the same chemicals which produced 90 (1+) reactions, 38 of 90 (42%) of the reactions were lost. The reasons for such non-reproducibility were not clear; however, Mitchell suggested that the initial patch test produced false positive reactions due to other concomitant positive reactions. He once again reiterated the term ABS and discussed the importance of retesting the suspected chemicals one at a time.

Maibach broadened the term to the excited skin syndrome (ESS) suggesting that it is the entire skin, not just the back, which is hyper-reactive. In the same paper, Maibach described an experiment in which he applied a neomycin-related antibiotic, every day, in a few volunteers to test the cumulative irritancy; petrolatum was used as a control. On the fifth day, some volunteers developed a strong vesicular reaction to the test antibiotic, at the same time, they developed a positive reaction to the petrolatum control. When these subjects were rechallenged with petrolatum some weeks later, none of them reacted. As allergic or irritant reactions to petrolatum are quite uncommon, Maibach claimed that these reactions were falsely positive due to ESS. He also reported that when a dilution series of antigen was applied one concentration at a time the threshold concentration required to elicit a positive reaction shifted to the right. Maibach et al. reported that 42% of previously positive reactions were lost when retested one at a time, thus strengthening their concept of ESS.

Bruyneel et al. reported that when 61 subjects who had previously shown multiple positive reactions were retested with allergens that previously elicited weak positive reactions, 44.3% of these reactions were lost. He noted that in patients whose eczema was clear, many previously strong positive reactions were also lost. In addition, he reported an increase in the number of positive reactions of challenges in close proximity to strong reactions. In another paper, Bruyneel et al. reported a new phenomenon, the spill-over effect. When marginally irritant concentrations of sodium laureyl sulphate (SLS) were applied at a fixed distance away from a strong positive allergic reaction, in 12 of 15 subjects, the intensity of reaction was significantly higher in SLS patches situated adjacent to the allergic reaction.

Interestingly, even before the invention of the terms ABS or ESS, Kligman and Epstein reported that skin which is repeatedly inflamed or is extensively involved in dermatitis often becomes hyper-reactive. Substances...
which normally cause no reaction may then incite irritant responses which can be mistaken for contact sensitization, this was named as conditioned hyperirritability. He also described another phenomenon called para-allergy, in which patch test reactions can become accentuated, as a result of strong positive reaction elsewhere. Magnusson and Hersle observed that if a reaction developed at the site of adhesive tape which is used to apply the patch test, a much greater frequency of positive reactions were seen.

However, in 1986, Kligman and Golldhausen presented results of a series of experiments contradicting all previous conceptions about ABS or ESS. They first obtained baseline responses in a number of volunteers using either irritants or allergens to which they were sensitive. Then, they generated strong responses with sensitizers such as dinitrochlorobenzene (DNCB), nickel sulphate (NiSO₄), or *rhus oleoresin* of poison ivy. First, they challenged eight volunteers with four patches of *rhus oleoresin*. Simultaneously, they applied two patches of SLS close to the rhus patches. The results showed that there was no change in the intensity of SLS reactions in the presence or absence of four strong allergic reactions. Secondly, they used NiSO₄ and *rhus oleoresin* in a similar experiment and showed that the intensity of responses to NiSO₄ did not alter in the presence or absence of four rhus patches. In the third study, they showed that strong reactions to DNCB did not alter the responses to irritant. Lastly, they rejected the idea of spill-over effect and showed that there was no change in the intensity of reactions at a close proximity or away from a strong reaction.

Bandmann and Agathos reported that only 8-6% of reactions were lost on repeat testing compared with 42% reported by Mitchell. However, the difference could be attributed to a slightly different methodology as they tested both strong and weak reactions. In a recent paper, Andersen et al. investigated the ABS using TRUE test NiSO₄ patches. Their results failed to demonstrate the ABS as the presence of multiple strong positive patch test reactions did not alter the skin reactivity.

It is evident from the literature that some subjects give multiple positive reactions to routine patch testing. However, the presence of ABS or ESS is not well understood and it is clearly debatable as to what factors contribute to production of multiple positive reactions. In order to study the phenomenon it is necessary to be able to reproduce it. Therefore, by presuming that ABS is a true phenomenon the following questions have been investigated in this study: (i) whether the ABS is a generalized augmentation of reactivity of skin; (ii) whether ABS is a purely localized effect; (iii) is ABS an individual-specific phenomenon; and (iv) is ABS in any way reproducible. Multiple positive reactions were produced on the back of normal controls, nickel-sensitive subjects and people with a previous history of ABS. A pseudo-angry back situation was created, so that alterations in skin reactivity threshold could be studied. Also, people exhibiting multiple positive reactions in the standard patch test clinic were tested to see whether any aspects of the ABS could be demonstrated or repeated.

**Materials and methods**

Thirty-two nickel-sensitive individuals, 11 subjects with previous diagnosis of ABS, and 16 non-sensitive individuals attending the dermatology out-patient clinics at the Royal Liverpool University Hospital were invited to participate — all gave informed consent. Serial fourfold dilutions of nickel sulphate hexahydrate (NiSO₄6H₂O) were made in yellow soft paraffin (YSP) to give final concentrations of 5, 1.25, 0.31, 0.07 and 0.01%. These were loaded into 5 ml syringes from which an approximately 5 mm length of ointment was applied to 8 mm Finn-chamber discs. Serial fourfold dilutions of croton oil (CO) (Sigma chemicals Ltd, Poole, U.K.) were made in YSP to obtain final concentrations of 3, 1, 0.3 and 0.1%. Each concentration was loaded into 5 ml syringes.

**Assessment of responses**

The patch tests were removed after 48 h and each site was scored visually according to the criteria of the ICDRG, no reaction: ±, doubtful reaction: +, weak (non-vesicular) reaction: ++, strong (oedematous or vesicular) reaction: ++++, extreme reaction. erythema was quantified by means of a reflectance instrument (Erythema Meter, Diastron, U.K.). Three sets of erythema meter readings were obtained at each challenge site. Control readings were obtained from the un-involved skin adjacent to the challenge site. An erythema index for each site was calculated by subtracting the mean of three erythema readings of the control site from the challenge site. The graphs are plotted using the erythema index.

**Irritancy potential of croton oil**

To obtain the irritancy potential of CO, four healthy volunteers were challenged for 48 h with a duplicate
dilution series of CO (3, 1, 0.3, 0.1%) on the back. The patches were removed after 48 h and each site was scored visually and with an erythema meter.

Studies to examine if angry back syndrome is a state of generalized augmentation of reactivity

The principle of the experiment was to see whether the presence of a strong positive patch test reaction could cause a change in the threshold concentration—the lowest concentration to elicit a positive reaction. The observation was made in 10 nickel-sensitive subjects to see whether, if present, it was a generalized phenomenon. First, to obtain the baseline threshold concentration for elicitation, the nickel-sensitive subjects were challenged with duplicate sets of Finn-chamber patches, containing three diluted concentrations (0.01, 0.07 and 0.31%) of NiSO₄·6H₂O in YSP. Stronger concentrations of 5% NiSO₄·6H₂O and 1.25% NiSO₄·6H₂O were omitted. The patches were applied across the mid back on either side of the vertebral column, with the highest concentration placed medially. The patches were removed after 48 h, and the lowest concentration to evoke a positive response (threshold concentration) was noted. Erythema was quantified with the erythema meter.

After an interval of 7 days, the challenge with low concentrations of NiSO₄·6H₂O was repeated in the presence of a large, strong positive allergic reaction to see whether there was a change in the response threshold. The same 10 nickel-sensitive subjects were re-challenged simultaneously with the three dilutions of NiSO₄·6H₂O, and also, to produce a strong positive reaction, with four patches of 5% NiSO₄·6H₂O applied on each corner of the back. The patches were removed after 48 h and threshold concentration was noted, and compared with the threshold concentration obtained in the absence of the strong positive reaction.

Studies to see whether angry back syndrome is a localized augmentation of reactivity

This aim of this experiment was to see whether the ABS could be generated as a local phenomenon in the vicinity of a large, strong allergic or irritant response. A strong positive reaction to an antigen or irritant (CO) was generated and a series of challenges with the threshold concentration (0.31%) was applied at increasing distances from the large reaction. In 18 known nickel-sensitive subjects the threshold concentration was established by challenge with a dilution series of NiSO₄·6H₂O from 0.01 to 0.31% as above. Then strong positive reaction was generated with 5% NiSO₄·6H₂O applied on four closely positioned Finn chamber discs. Simultaneously, live Finn chamber discs bearing the threshold concentration of NiSO₄·6H₂O were placed across the back at increasing distances (2.5 cm apart) from the strong challenge.

Twelve normal healthy control subjects were challenged with 1% CO applied on four closely positioned Finn chamber discs to generate a large, strong positive irritant reaction. Simultaneously, live Finn chamber discs bearing the threshold concentration of CO (0.3%) were placed across the back at increasing distances (2.5 cm apart) from the strong challenge. Four subjects received heterologous challenges in a similar way, comprising 5% NiSO₄·6H₂O in two, or 1% CO in two, and the reciprocal threshold concentration of 0.3% CO and 0.3% NiSO₄·6H₂O.

Studies to see whether angry back syndrome is an individual specific phenomenon

This study was designed to explore the possibility that the ABS is not a general phenomenon but one which occurs only in certain individuals. Six subjects with a history of ABS upon routine patch testing and known sensitivity to NiSO₄·6H₂O took part in this study. First, they were challenged with duplicate sets of Finn chamber patches containing three low concentrations (0.01, 0.07, and 0.31%) of NiSO₄·6H₂O in YSP, as described in the previous experiment. After an interval of 7 days, a large strong positive reaction was elicited and the dose–response challenge repeated as described above to see whether there was a change in the response threshold. Secondly, to examine whether these subjects with a previous history of ABS are more sensitive to local effects of a strong positive reaction, a strong positive reaction to NiSO₄·6H₂O was generated on day 7 and a series of challenges with the threshold concentration of NiSO₄·6H₂O was applied at increasing distances from the large reaction as described in the previous experiment.

Studies to see whether angry back syndrome is a reproducible phenomenon

To examine the reproducibility of ABS, five subjects who were previously diagnosed as exhibiting the ABS were re-challenged with the identical battery of allergens to which they had shown multiple reactions in the past.
Results

Irritancy potential of croton oil

Since CO was to be used to produce both weak and strong irritant reactions, it was therefore necessary to establish the nature of the dose–response relationship for this compound. Challenges with 3 and 1% CO produced strongly positive reaction in four of four subjects tested; two subjects had blistering reaction to the 3% challenge. Challenges with 0.3% CO produced weak positive reactions in four of four subjects, while 0.1% CO produced very weak reaction in only one subject. The threshold concentration of CO to produce a positive reaction was thus 0.3% in three of four subjects and 0.1% in one of four subjects.

Studies to see whether angry back syndrome is a state of generalized augmentation of reactivity

The baseline threshold concentration to elicit a positive reaction was 0.31% NiSO\(_4\).6H\(_2\)O in seven of 10 subjects, 1.25% in two of 10 subjects and 0.07% in one of 10 subjects. In six of 10 (60%) subjects, the threshold concentration of NiSO\(_4\).6H\(_2\)O did not alter in the presence of strong positive patch test reactions. In three of 10 (30%) subjects the threshold concentration was higher in the presence of strong positive reactions, while in one subject, the threshold concentration was lower in the presence of strong positive reactions. Erythema readings of the patch test responses were slightly lower in the presence of strong positive reactions (Fig. 1). Overall, these results indicate that no specific pattern of hyper-reactivity of skin was evident in the presence of strong concentrations of NiSO\(_4\).6H\(_2\)O.

Studies to see whether angry back syndrome is a localized augmentation of reactivity

In the presence of a large, strongly positive allergic reaction, responses to all five replicate challenges with the threshold concentration of NiSO\(_4\).6H\(_2\)O placed at increasing distances, were identical in 10 of 18 nickel-sensitive subjects. In three of 18 subjects the responses further away from the strong positive reaction were slightly higher, in two of 18 subjects the responses were higher close to the strong positive reaction while in the remaining three of 18 subjects the responses were higher in the middle. Erythema readings were, as expected, higher at the strong positive reactions than at the threshold concentrations. There was slight
variability in the erythema readings at the repeat challenge with the threshold concentration (Figs 2 and 3).

In the presence of a large, strongly positive irritant reaction to CO, seven of 12 normal controls gave identical responses to all five replicate challenges with the threshold concentration of CO. In four of 12 subjects the responses furthest away from the strong positive reaction were slightly higher, in the remaining one subject the responses were higher in the middle. The strong positive reactions gave expectedly greater erythema meter readings than at the threshold concentrations. There was only slight variability in the erythema readings of multiple challenges with the threshold concentration (Figs 2 and 4). The four subjects who received heterologous challenges showed similar reactions; there was slight variation in the responses at the threshold concentration, but there was no consistent trend. The results from these experiments show that the skin adjacent to strong patch test reactions does not behave in an unpredictable manner and there was no evidence of localized hyper-reactivity.

Studies to examine if angry back syndrome is an individual-specific phenomenon

To examine the possibility that the ABS is an individual-specific phenomenon, the experiments were repeated in subjects with a previous history of ABS. The baseline threshold concentration to elicit a positive reaction was 0.31% NiSO₄·6H₂O in four of six subjects and 1.25% in two of six subjects. In all six subjects, the threshold concentration of NiSO₄·6H₂O did not alter in the presence of strong positive patch test reactions.

Secondly, in the presence of a large, strongly positive allergic reaction, four of six subjects gave identical responses to all five replicate challenges with the threshold concentration of NiSO₄·6H₂O. In the remaining two subjects there was slight variation in the responses, but there was no consistent trend. The above experiments indicate that subjects with a history of ABS did not react in an unpredictable manner. It is also clear that ABS is not an individual-specific phenomenon.

Studies to see whether angry back syndrome is a reproducible phenomenon

Five subjects with the previous history of ABS were re-challenged with the patch test series to which they gave multiple positive reactions in the past. All five subjects gave fewer positive responses than their initial patch test challenge. All subjects were still allergic to multiple allergens (more than five) but some reactions were lost. The experiment failed to reproduce ABS.

Discussion

When the work was commenced, the starting presumption was that the ABS was a real phenomenon that would be readily reproduced and hence subject to analysis. However, the studies described have shown that the ABS or ESS could not be reproduced with any group of subjects tested such as, nickel-sensitive subjects, people with a previous history of ABS or normal healthy individuals. The first experiments were designed simply to confirm the widely held belief that the presence of one strong patch test reaction would induce an alteration in the reactivity, resulting in multiple concomitant reactions as proposed by...
Mitchell. However, it is evident from this study that the presence of strong positive reactions could not produce a state of generalized hyper-reactivity of the skin. When subjects were challenged with a dilution series of NiSO₄·6H₂O in the presence of other strong reactions on the back, the threshold concentration of NiSO₄·6H₂O remained unaltered.

Also, no evidence was found that the presence of one strong positive reaction to an allergen or irritant could increase the skin reactivity in a local fashion. Furthermore, there was no evidence of so-called spill-over effects; a phenomenon described by Bruynzeel et al. in which the intensity of reactions increases adjacent to a positive reaction. As would be expected, some variability was observed in the responses at a threshold concentration. However, the variation was not uniform and did not show any particular trend with distance away from a large challenge reaction.

As the ABS could not be shown to occur as a general phenomenon in a group of 10 subjects with contact sensitivity to nickel, the possibility was examined that ABS could be a phenomenon found only in certain predisposed individuals. Hence, subjects who show multiple positive patch test reactions may have naturally hyper-reactive skin. Volunteers with a previous history of ABS were subjected to similar tests as described above and the results were identical to the overall findings that a strong positive reaction could not increase local or general reactivity threshold of the skin. Moreover, when these subjects were challenged with a series of allergens, they still produced multiple positive reactions which suggests that they are indeed genuinely allergic to multiple allergens.

There is no doubt that one often sees patients who give multiple positive reactions to which no relevance can be given. The question arises then of what is the ABS? The literature about ABS is poorly defined, full of vague statements and far from conclusive. Mitchell and Maibach put forward their hypothesis that ESS is not a form of delayed hypersensitivity, as it can be brought on by non-immune irritation. However, the main weakness of their experiments is that they used a single concentration of the allergen for retesting rather than the dose--responses which would have shown any shift in the threshold concentration.

Bruynzeel and Maibach indicated their own practice that when more than one positive reaction is present, they immediately suspect ABS unless otherwise proven. Their immediate action is to retest the history, and if the relevance of positive reactions could not be established, they conclude the presence of a false positive reaction. Although, it is some times difficult to establish the relevance of all the positive reactions such examples demonstrate the potential lack in the understanding of ABS. Hence, if one sees a patient with multiple positive reactions, there are no set criteria to suggest how many reactions are necessary to be confident that the patient is exhibiting the ABS. Should a subject with five positive reactions be suspected of ABS as much as a subject with 15 positive reactions?

Various researchers have suggested that pre-existing eczema could be an explanation for the findings of false positive reactions. Maibach discussed in his chapter that even Jadassohn shortly after he developed the diagnostic patch test, was aware that patients with active eczema gave stronger patch test results. Geiger reported that when he applied 60% turpentine to eczema patients and controls, 90% of eczema patients reacted compared with only 6% of normal control. However, at a lower concentration of 30% turpentine there was no difference between the two groups. Grobnick demonstrated that the skin at the site of eczema is more reactive than normal skin: he challenged subjects with an antigen to which they were previously allergic. One to 2 months later when the challenge site was completely healed, the same subjects were re-challenged with an allergen to which they were not allergic. He showed that subjects gave a positive reaction at the previous eczema site but not on the control site.

In the present study two of six subjects with a previous history of ABS or multiple positive reactions had active eczema; however, no evidence of hyper-reactive skin was found in those subjects. Memon and Friedmann have shown that the immune system exhibits very reproducible responses, although, at the threshold concentration of an antigen some variability in the responses was observed. One possible but unlikely explanation for non-reproducibility of multiple positive patch test reactions, some of which were weak reactions, could be that the concentrations of those allergens may be at or near the threshold concentration and hence subject to variability. However, further studies are necessary to confirm this hypothesis. It may be possible that the people with multiple positive reactions may genuinely be sensitive to a number of allergens, the present studies failed to find any evidence for the existence of a state of non-specific hyper-reactivity.

The studies presented in this paper were surprising to us because they seem to contradict the clinical dogma. First, none of the manoeuvres employed appeared able to alter cutaneous reactivity and hence, it can be
concluded that the ABS was a non-reproducible phenomenon. Secondly, one strong positive reaction does not generally influence the skin reactivity as it neither increased the local reactivity of the skin nor caused a general shift in the reaction pattern. Thirdly, ABS was not found to be an individual specific phenomenon as people with a previous history of ABS did not behave differently on repeat testing in presence or absence of a strong positive reaction. However, on repeat testing they lost some previously positive reactions. The only way in which the findings presented here can be related to the clinical dogma is if ABS is a transient state of hyper-reactivity of skin. This still does not explain why some authors claim to have succeeded in altering the skin reactivity. However, until some means are found to alter the reactivity of skin, the confirmation of the existence of this phenomenon and of any underlying mechanisms, must be the subject of future research.

References

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