The 'autoimmune screen'

More informed but no more enlightened

Mark H Arnold

THE SUBJECT OF SCREENING and its usefulness is often debated. Recently, the concept of blanket immunological screening for the presence of 'autoimmune disease' was explored in the *Australian Journal of General Practice*.[1] Chan and Keat observed that, 'In our unpublished audit, some clinicians felt that symptoms or signs of the nature of fatigue, arthralgia or rash warranted an "autoimmune screen"'. This comment begs the question: When considering the reasons why people might present with one or other of these symptoms or signs, what do we expect the outcome of 'autoimmune screening' to be? Specifically:

- What sorts of tests can be considered to be useful for screening?
- Is ordering any test likely to confirm or refute a diagnostic possibility validly arrived at by the hypothetico–deductive process?
- What is the likelihood of the posited diagnosis or diagnoses one is attempting to screen for?
- What is the sensitivity and specificity of the test/s?
- Will the test/s give a false positive or false negative result to which one might assign inordinate diagnostic weight?

In other words, will the results of an 'autoimmune screen' leave you no more enlightened as to the nature of the patient's problem? Will the results be unexpected and prompt further assessment driven by the need to explain this result to the satisfaction of the patient?

Many immunological tests have relatively high specificity for disease, such as cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA/anti-PR3) for granulomatosis with polyangiitis (previously known as Wegener granulomatosis) and antiglomerular basement membrane antibodies in Goodpasture syndrome; however, high test-specificity for rare diseases does not equate with efficacy as a screening tool for the explication of undifferentiated symptoms. The usefulness of many laboratory tests as appropriate screening tools is therefore questioned,[2] and important concepts include normal ranges for continuous variables such as the rheumatoid factor, as distinct from categorical variables such as antinuclear antibody (ANA) titres where the 'cut point' for normality is hard to establish, debatable and dependent on the nature of the assay. In the case of the ANA it is not simply the titre of the result but also the pattern of the ANA that has considerable diagnostic significance.

Hence, lumping these tests together as a 'global screening tool' (typically including a check on the patient's human leukocyte antigen B27 [HLA-B27] status) for undifferentiated symptoms is epistemically flawed since finding an abnormal autoantibody result in the absence of a suggestive context will not confirm the presence of a disease. These diseases are also differentiated from one another through the application of basic clinical logic.

A review of the most recent Medicare Benefits Schedule indicates that if the ANCA, HLA-B27, C3 and C4, ANA, DNA binding and extractable nuclear antigens (ENAs) are requested at the 85% rebate level, the taxpayer will be charged $183.45.[3] This 'autoimmune screen' or 'panel' is commonly requested (or has been performed) when patients are referred for a rheumatological consultation.

Patients with non-inflammatory lower back pain, non-specific arthralgia, non-specific fatigue and, on occasions, nodal osteoarthritis are often subjected to these tests in apparent disregard for the fact that for conditions with a low pre-test probability, the positive predictive value of a positive 'screening' test for such conditions is vastly lower than when 'screening' for conditions with a high pre-test probability.

There are several fundamental concepts that must be appreciated when assessing patients with musculoskeletal complaints. These are:

- Rheumatological diagnoses are made by history and physical examination. Physical examination will reveal a pattern of joint involvement that reflects conceptually distinct rheumatic disease phenotypes.
- Rheumatological disease phenotypes allow us to recognise that – in the main – there are clear distinctions between what things constitute a conclusion of osteoarthritis, HLA-B27-associated spondyloarthritis, systemic lupus erythematosus (SLE) and ANCA-associated vasculitis; inherently, these are different disease entities.
- Rheumatological diagnoses cannot be made purely by isolated test results that do not reflect the patient context.

Osteoarthritis is very common, many inflammatory rheumatic diseases are quite common, but most of those supposedly identified by the 'autoimmune screen' are distinctly uncommon; without a suggestive history and examination, there is a low pre-test probability of a condition being present. A very basic working knowledge of rheumatic disease epidemiology is necessary. When sex and age are not considered (which is often the case when an 'autoimmune screen' is ordered), the following statistics are seen:

- hip and knee osteoarthritis has a prevalence of approximately 4.5%[4]
- the prevalence of rheumatoid arthritis is approximately 2% of the population[3]
- approximately 8% of the population is HLA-B27 positive, and of those 8%, approximately 14% will have spondyloarthritis[5]
- the prevalence of SLE varies between 20 to 150 cases per 100,000 people – practically approximately 1:1000[6]
- the prevalence of ANCA-associated vasculitis (eg granulomatosis with polyangiitis) is no more than 160 per million people.[7]

The pre-test probability of a person without suggestive symptoms and signs of SLE or ANCA-associated vasculitis is, respectively, 1:1000 and 16:100,000. Far more often than not, people without suggestive signs and symptoms of such conditions who are ANA or ANCA-positive will have a false positive result.

The following clinical points are also fundamental:

- neither lower back pain of the non-inflammatory type nor nodal osteoarthritis are manifestations of rheumatoid arthritis, SLE or ANCA-associated vasculitis
- isolated fatigue and widespread chronic non-articular pain are not, in isolation, indicative of rheumatoid arthritis, SLE or ANCA-associated vasculitis
- multiple medically unexplained symptoms are not typical manifestations of rheumatoid arthritis, SLE or ANCA-associated vasculitis.

Hence, performing an 'autoimmune screen' (with an HLA-B27) in the above scenarios will result in spurious, false-positive results in almost all cases.

The Australian Rheumatology Association has recently advised against undertaking serological testing in patients with a low likelihood of SLE.[8] Furthermore, the American Medical Association's yearly 'Update(s) on medical overuse' highlights a medical culture of 'doing everything', and that 'overuse stems largely from the misinterpretation of clinical evidence.'[9] In the 2015 'Methods to avoid overuse' it was noted that 'at least one-third (range: 31–37%) of symptoms did not relate to an identifiable disease. Approximately 73% (range: 56–94%) of diagnoses are based on the history and an additional 4–17% on the physical examination. There is considerable overlap between physical and psychological symptoms, and approximately 75% (range: 71–79%) of symptoms improved in weeks to months.'[9] The authors concluded that the implications are that clinicians should be cautious when ordering 'diagnostic tests to identify disease without high pre-test probability because most disease can be diagnosed with a thoughtful history and skillful physical examination'.[9]

Though it may be a convenient shorthand, it serves no clinical purpose to order an 'autoimmune screen' without having determined that any of these tests will confirm or refute the presence of a condition through the usual hypothetico–deductive process. Repetitive or serial ordering of an 'autoimmune screen' – particularly if this includes an HLB-B27 – is illogical and rarely leads to a change in diagnosis or management. It does typically lead to a referral for a retrospective explanation of positive test results rather than for confirmation or refutation of the presence of a rheumatic disease.

Referrals for a retrospective explanation of positive test results thought to imply a specific diagnosis are a post-hoc ergo propter hoc logical fallacy; it assumes that the test result has a causal/logical relationship with the clinical problem it (supposedly) follows: 'Ms Smith has some symptoms not representative of SLE; we tested her ANA and it is positive … so she has lupus.' Ultimately, if no such disease is identified (since it does not exist), these are false positive results.

Such requests increase appointment waiting times, exacerbate patient anxiety, and increase personal and taxpayer health expenditures. Importantly, testing does not reassure patients, since 'many persons have screening undertaken without understanding precisely what the test is for, the accuracy of the test, and the implications of any possible test results. These are the roots of many of the potentially avoidable adverse psychological consequences of screening'.[10]

Undertaking an undirected 'autoimmune screen' for conditions with a low pre-test probability must be discouraged. Screening with immunological tests is not a proxy for the rational process of formulating a differential diagnosis. Responsible test ordering should be undertaken to confirm (or refute) differential diagnostic possibilities that can be validly justified by rational argument.

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