

HYPOTHESIS

Nodal generalised osteoarthritis is an autoimmune disease

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Nature of osteoarthritis

Osteoarthritis (OA), the commonest abnormality to affect synovial joints, has accompanied man throughout his evolutionary history, and a similar process occurs in other animals that fuse epiphyses in the adult.¹⁻³ Such prevalence and phylogenetic preservation suggest that OA is a *process* rather than a *disease*, reflecting the response of articular tissues to extrinsic or intrinsic insult, or both.^{4,5} The recognised synthetic activity of osteoarthritic tissues,⁴⁻⁶ the radiographic remodelling and favourable outcome seen in many patients with OA,⁷⁻⁹ and the prevalence of asymptomatic 'disease'^{3,10,11} support the concept of OA as a *repair process*.^{4,5} Like any repair process, OA may succeed or fail when responding to a variety of triggering or perpetuating insults (fig 1). The pathogenesis and variability of OA are poorly understood, but multiple factors, including genetic, constitutional, and environmental, are likely to play a part.^{3,12,13} Marked variability in the nature and chronicity of the insult(s), and host differences in effective repair response, result in the confusing heterogeneity of radiographic and clinical manifestations.

The 'subset' of nodal generalised OA (NGOA)

In an attempt to understand OA better and to identify factors initiating and influencing compensation (no symptoms, good outcome) or decompensation (symptoms, functional impair-

ment, 'joint failure'), OA has been increasingly divided into clinically determined subsets.³ Such categorisation has been by distribution of joint disease (generalised, pauciarticular, monoarticular¹⁴); predominance of certain radiographic features ('atrophic', 'hypertrophic'¹⁵); associated crystal deposition (pyrophosphate arthropathy,¹⁶ apatite associated destructive arthritis¹⁷); and presumed aetiological factors—for example, epiphyseal dysplasia, Kashin-Beck disease. Such subsetting, especially for common forms of OA, has proved problematic because of overlap,^{16,18} temporal transition from one subset to another,^{16,19} and difficulties in radiographic interpretation and crystal identification.¹⁹⁻²¹ Nevertheless, several groups are generally accepted.³

Nodal generalised OA, the best recognised subset, is characterised by polyarticular hand OA (principally interphalangeal and first carpometacarpal joints), female preponderance, early symptomatic inflammatory component, and Heberden (with or without Bouchard) node formation, or both^{3,14,22}: of all OA subsets, familial tendency is particularly recognised.¹³ Erosive OA is a less common generalised subset sharing many features of NGOA but differing in having marked subchondral erosive change, a more florid and prolonged inflammatory component, and a tendency to intra-articular osseous fusion.^{3,23,24} Minor subchondral erosions in NGOA, however, are not uncommon and whether erosive OA is a discrete subset or merely the more severe end of the NGOA spectrum has been questioned.²⁵ Many elderly subjects have patchy hand interphalangeal OA or nodes: this may relate to obvious prior trauma, but is often asymptomatic and apparently sporadic. Although there is no sharp division between such hand OA and NGOA, the latter is classically symptomatic in middle age, presenting as a stuttering-onset 'monoarthritis multiplex', is unrelated to obvious trauma, and affects most if not all rays. At sites other than the hand, such as the hip, the tendency to bilateral disease and to diffuse (concentric/central) rather than focal (superolateral) cartilage loss^{26,27} further supports the separation of NGOA as an inflammatory subset of OA.

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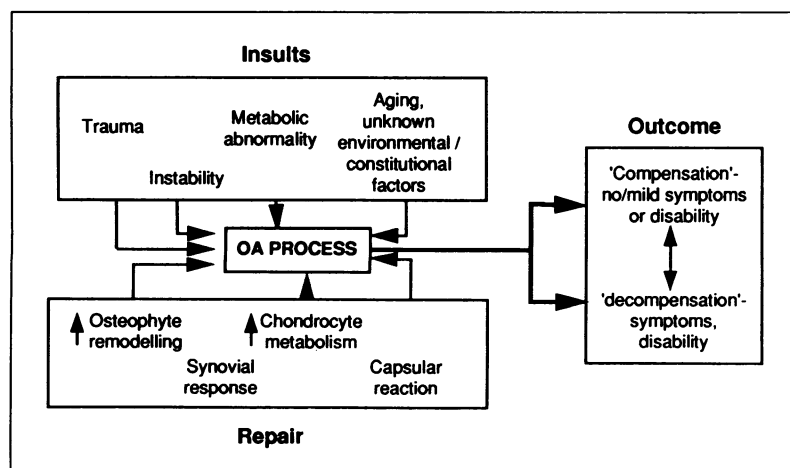


Figure 1 Representation of osteoarthritis as a repair process that may compensate or fail in response to a variety of insults.

Genetic associations

Surprisingly, despite marked familial predis-

position, few studies have searched for genetic markers in NGOA.¹³ Until recently only four studies had examined the frequencies of HLA antigens, with conflicting results: Lawrence *et al* reporting increased frequency of HLA-A1B8,²⁸ Brodsky *et al* an increase in HLA-B8,²⁹ and two studies finding no associations.^{30 31} A recent large study by Patrick *et al*, however, confirmed increased frequency of HLA-A1B8 in 90 unrelated patients with NGOA (relative risk compared with reference population 2.79; $p < 0.01$); an independently increased frequency of the MZ α_1 antitrypsin phenotype was also shown (relative risk 3.7; $p < 0.01$).³² Although in theory relative α_1 antitrypsin deficiency might enhance enzyme related joint tissue damage and thus promote development of OA, occurrence of normal α_1 antitrypsin concentrations in all patients favoured genetic linkage rather than protease inhibitor deficiency. Both the HLA and α_1 antitrypsin associations related to development rather than severity as judged by radiographic hand OA scores. Interestingly, a subgroup with erosive OA had both higher radiographic scores (corrected for the presence of erosions) and increased frequency of the MS α_1 antitrypsin phenotype ($p < 0.001$), perhaps supporting the concept of erosive OA as severe NGOA with additional genetic factors influencing severity.

These findings are of particular interest as HLA-A1B8 is in linkage disequilibrium with DR3 and commonly associates with conditions in which an autoimmune component is well recognised—for example, systemic lupus erythematosus,³³ autoimmune thyroid disease,³⁴ Sjögren's syndrome.³³ An association with a particular α_1 antitrypsin phenotype may also be relevant to an autoimmune pathogenesis because α_1 antitrypsin is encoded on chromosome 14 near the Gm locus for IgG,³⁵ and it is conceivable that genetically determined variability in immunoglobulin heavy chain morphology could predispose to autoimmune phenomena and resultant disease.^{36–38} Investigation of Gm allo-types, or other more directly involved gene products in linkage with α_1 antitrypsin on chromosome 14, might therefore be of relevance in NGOA.

Other studies have concentrated on genes relating to collagen formation on the assumption that inherent defects of particular forms of type II collagen may predispose to biomechanical faults in cartilage and 'decompensation' under normal mechanical loading. Palotie *et al* recently described two Finnish families with premature 'generalised OA'.³⁹ Using restriction fragment length polymorphisms within and around the type II collagen gene on chromosome 12, they noted linkage between the cartilage specific gene (COL2A1) and the development of arthritis, supporting the primacy of cartilage structure (specifically the collagen network) in development of 'joint failure'. Although clinical details were sparse, the age of onset, distribution, and autosomal dominant inheritance favoured dysplasia rather than NGOA. Hull and Pope reported increased frequency of a closely situated restriction fragment length polymorphism (*BamHI*) in a group

Observations which support autoimmune mechanisms in nodal generalised osteoarthritis

Genetic associations:

HLA-A1B8
 MZ α_1 antitrypsin
 Female preponderance
 Perimenopausal onset
 (Hormonal influence on disease expression)
 Association with other autoimmune disease
 Sjögren's syndrome (erosive osteoarthritis only)
 Thyroid disease
 Immunological findings in synovium and cartilage
 Increased frequency of rheumatoid factor

of women with OA affecting more than one joint before age 60,⁴⁰ though a study of COL2 genes in a large number of English patients with well defined NGOA failed to show any associations (Priestley L, Fergusson C, Ogilvie D, *et al*, unpublished data), thus questioning the relevance of collagen genes to the NGOA subset. In summary therefore, the genetic information available for NGOA concurs only to suggest that immune mechanisms might be involved in its pathogenesis.

Hormonal influence on disease expression

What further support is there for the possibility that NGOA is an autoimmune disease? In addition to shared genetic (HLA) associations, two common characteristics of autoimmune disease are female preponderance and hormonal influence on disease expression (table). Symptomatic NGOA is principally a female condition with onset commonly around the menopause: indeed this association is so striking it was previously labelled 'menopausal arthritis'.⁴¹ No such association with non-nodal OA has been made, again supporting separation of NGOA as a distinct subset.

The influence of sex hormones on development of OA, including a suggested relation with previous hysterectomy,⁴² has recently been reviewed.⁴³ The positive associations with obesity, perimenopausal onset (changing sex hormone profiles), fibroids, and dysfunctional uterine bleeding, and the negative correlation with osteoporosis may all be explained by an absolute or relative oestrogen excess.⁴³ Support for this comes from certain animal models of OA which show deterioration with oestrogens and improvement with tamoxifen.⁴⁴ Suggested mechanisms usually emphasise the direct hormonal effects on cartilage matrix homeostasis^{43 44}: this is not altogether surprising as cartilage, rightly or wrongly, remains the main focus for research interest in OA.⁴⁵ An equally valid interpretation, however, is that hormonal fluctuation/imbalance may predispose to NGOA through modulation of the immune system rather than by connective tissue activity, there being abundant evidence for hypoandrogenic/hyperoestrogenic states being contributory to development or exacerbation of 'autoimmune disease' through such effects.⁴⁶

Autoimmune disease associations

An association with other autoimmune phenomena would obviously strengthen the case. Although the question of autoimmunity in

NGOA has not been specifically considered, several observations offer tantalising clues. An increased prevalence of autoimmune thyroid disease was reported in a controlled study of patients with pyrophosphate arthropathy, most of whom were women, many with NGOA^{9 47}: the lack of an association between hypothyroidism and chondrocalcinosis⁴⁸ suggests that this might have arisen through association with NGOA. The reported association between Sjögren's syndrome and erosive OA⁴⁹ is also of interest, particularly if erosive OA is a severe rather than separate form of generalised OA.⁵ Similarly, the increased frequency of rheumatoid factors in NGOA^{14 50} may reflect an autoimmune diathesis. Controlled studies determining frequencies of organ specific antibodies, rheumatoid factors, and autoimmune disease in NGOA would thus seem warranted.

Immunohistochemical evidence

The increasingly recognised inflammatory component in OA,^{51 52} and immunohistological studies of OA synovium and cartilage⁵²⁻⁵⁶ lend further support to the involvement of immune mechanisms in pathogenesis. It is possible of course that the finding of immunoglobulin (particularly IgA), complement, and 'immune complexes' in OA cartilage,^{22 52 56} and the identification of lymphoid and mononuclear populations in OA synovium (identical with, though less widespread than those found in rheumatoid arthritis^{52 53 55}), reflect merely non-specific reaction to tissue damage rather than inflammation driven primarily by immunological events. Nevertheless, it is of interest that such cartilage and synovial abnormalities (at the hip) are more common and pronounced in 'primary' polyarticular NGOA than in 'secondary' pauciarticular OA,^{22 52} again supporting the possibility of a systemic (? primary) rather than just local (secondary) inflammatory reaction.

Although cartilage might enjoy the status of immunological privilege by virtue of its anatomic structure, autoimmunity to cartilage might theoretically develop if sequestered antigens were exposed or became autoantigenic by interaction with exogenous or intrinsic factors. Anticollagen antibodies and cell mediated immune responses to collagen have indeed been shown in patients with OA, but also in patients with acute joint trauma and inflammatory joint disease.^{57 58} Whether or not such immune responses play a part in perpetuation of joint disease, their lack of specificity favours a secondary rather than primary role in causation. If autoimmunity plays a part in NGOA it is most likely to exert its initial inflammatory effects on non-cartilaginous articular tissues. From a clinical standpoint the synovium/capsule (or even bone) would seem a likely target.

Single shot insult

As in all arthropathies the distribution of joint disease in NGOA remains unexplained. Hypotheses to explain preferential distribution include differing mechanical forces at different sites^{59 60}

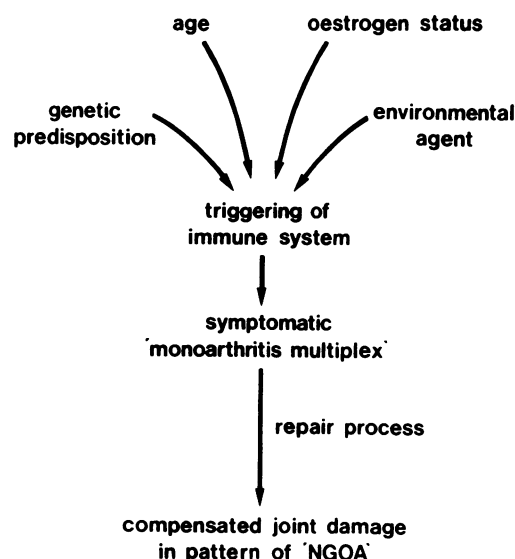


Figure 2 Outline of nodal generalised osteoarthritis (NGOA) as an autoimmune disease.

and effects on joint design resulting from varying rates of evolutionary change.⁶¹ The bilateral, 'symmetrical' distribution of NGOA is also unexplained. Although the role of neurogenic factors in the symmetry of inflammatory joint diseases has been discussed,⁶⁴ an alternative hypothesis for autoimmune based disease relates to the selectivity of pathways undertaken by circulating lymphocytes, which limits the distribution of immune mediated disease.⁶³ The symmetry and distribution of disease might thus primarily reflect predetermined 'homing' of lymphocytes rather than targeting determined by local events—for example, mechanical insult and usage.⁵⁹

A generally good prognosis has recently been confirmed by a controlled study of patients with established NGOA which showed that compensated OA has little symptomatic or functional impact on the aging hand.⁶⁴ If symptomatic NGOA is an autoimmune condition it would thus seem to be a selective 'single shot' disease affecting target joints of genetically predisposed subjects at a time conditioned by age, hormonal and other constitutional factors. There is increasing evidence that many autoimmune diseases are triggered by external (predominantly infective) agents,^{65 66} and an unidentified external trigger for NGOA may exist. Whatever its nature, this immune mediated joint insult triggers a hypertrophic repair process which, despite marked cartilage loss, then usually compensates in terms of symptoms and function. Once the inflammatory phase has settled the patient is left with architecturally abnormal joints, which we recognise as 'OA' (fig 2).

Inclusion of NGOA within the autoimmune umbrella may further stimulate interest in what has previously been regarded by some as an unexciting 'degenerative' condition. From currently available information it would seem that further studies of genetic, constitutional, and immunological factors are warranted if we are to improve our understanding of NGOA, and hence the inherent repair process of synovial joints.

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