DEFINITION

1. **Rheumatoid arthritis** is a systemic disease which in fact affects many organs. In most cases of rheumatoid disease the synovial (mobile) joints are predominantly affected, by **chronic inflammatory synovitis**. The diagnosis is based on both clinical observations and laboratory tests.

CLINICAL MANIFESTATIONS

2. Rheumatoid arthritis has many manifestations. In about 70% of cases, it begins with insidious pain, stiffness and symmetrical swelling of the small joints. In about 20% of cases, persistent joint disease may be preceded by repeated self-limiting episodes (palindromic onset). About 10% have an explosive onset and, paradoxically, seem to do better in the long term. A small minority have generalised muscle pain long before arthritis (polymyalgic onset).

3. The joints most often first affected are those of the fingers - notably the proximal interphalangeal and metacarpophalangeal joints, shoulders, feet and wrists. It is usually a **distal, symmetrical, polyarthritis.** The knee is involved first in only 3% of cases. The arthritis often affects the cervical spine, temporomandibular (jaw) and cricoarytenoid (larynx) joints. Particularly in middle-aged men, the first symptoms may not be in the joints. It may present with malaise, fatigue, anaemia, myalgia, breathlessness or weight loss.

4. Onset can be at any age but the peak incidence is in the 5th decade. The clinical pattern and severity of the disease do not relate obviously to the age of onset. The course of the condition is very variable. Many patients have an episodic illness but others suffer slow, relentless deterioration, developing characteristic severe joint deformities.

5. Rheumatoid skin nodules occur in 25-30% of patients. They are not in themselves serious but tend to indicate extensive disease.

6. Extra-articular manifestations are frequent, may precede the onset of joint problems, may occur in any system and range in severity from the trivial to life-threatening.

    6.1. **Lymphadenopathy** (swollen glands) is not uncommon.

    6.2. **Lung** involvement may occur. Most commonly this takes the form of pleuritis but lung nodules, diffuse interstitial fibrosis or fibrosing alveolitis may occur. Caplan’s syndrome is a combination of rheumatoid lung nodules with massive fibrosis occurring in the pneumoconioses.

    6.3. **Heart** involvement is more common in men, often with asymptomatic pericarditis or thickened valves, sometimes found only at post mortem examination.

6.4. Generalized **osteoporosis** (thinning and weakening of bone) is often associated with active rheumatoid arthritis, as is **myositis** (inflammation of muscle) and **muscle atrophy** (wasting and weakening).

6.5. **Skin** involvement may include cold clammy hands, sometimes resembling Raynaud's phenomenon, and various other signs of rheumatoid **arteritis** (inflammation of arteries), including splinter haemorrhages in nail folds and painful skin **ulcers** which may get infected. **Purpura** (bleeding into the skin) may result from leucoclastic (with disrupted white blood cells) vasculitis.

6.6. **Eye** involvement may occur. **Scleritis** (deep inflammation of the wall of the eye) due to vasculitis is common. It is painful, and can cause blurred vision and even blindness if it extends. Episcleritis is a far les serious surface inflammation. **Sjogren's syndrome**, milder than in the idiopathic type, may be seen in rheumatoid arthritis. The symptoms are pain, redness and grittiness of the eye and photophobia, commonly with salivary gland enlargement also.

6.7. A moderate **anaemia** is almost always present in active phases of the disease and about a quarter of rheumatoid patients have **splenomegaly.**

6.8. Neurological complications occur, of which **nerve entrapment** is the most common, usually related to proliferative synovitis, eg causing carpal tunnel syndrome and ulnar nerve compression at the elbow. Other neurological complications can include mild sensory neuropathy with little weakness, autonomic neuropathy and severe peripheral neuropathy or mononeuritis multiplex resulting from vasculopathy.

7. Other potentially serious complications include:

7.1. **Infections**. Anecdotal evidence suggests that exacerbations of rheumatoid arthritis may be triggered by infection. Septic arthritis, although uncommon, can occur, especially in patients on corticosteroids and other immunosuppressant drugs.

7.2. **Cervical spine**. Rheumatoid involvement of the neck can be demonstrated by X-ray in about 80% of patients but is often asymptomatic, even when it causes subluxation (partial dislocation of vertebrae). Fortunately, although up to 1/3 of patients attending hospital with rheumatoid can be shown to have some degree of subluxation, it causes neurological symptoms in less than 1/3 of them. Interpretation of consequent limb weakness and pain can be difficult in a patient with widespread rheumatoid. Male patients are at greater risk of cord compression, which can even be fatal.

7.3. **Fractures**. Severe rheumatoid arthritis is always associated with osteoporosis. Stress-induced fractures resulting from minimal trauma may occur.

7.4. **Rupture of ligaments and tendons**. Local rheumatoid involvement may cause ligament or tendon rupture. Most often, this affects the tendons of the fingers, although the wrist and shoulder tendons may also be involved.

7.5. **Amyloidosis**. Rheumatoid arthritis can cause secondary amyloidosis, the harmful deposition in organs and tissues of an abnormal protein, which can be found by biopsy in about 10% of patients. It is a complication of many chronic infective and inflammatory diseases.

7.6. **Felty's syndrome**. This consists of splenomegaly and neutropenia, frequently with other complications, in those suffering from rheumatoid arthritis. It is associated with the presence of an antigen called DW4.

AETIOLOGY

8. Rheumatoid arthritis is a disease of complex multifactorial cause with an important genetic component. Current thinking is that interaction between genetic factors, sex hormones and an infectious agent initiates an autoimmune mechanism which culminates in a disease with inflammatory and destructive features.

8.1. **Genetic Factors**. The importance of heredity in rheumatoid arthritis has long been recognised. The condition is far more common in first degree relatives of sufferers (about 15% prevalence with sero-positive erosive arthritis) than in the general population. The concordance rate is six times higher in identical than in non-identical twins but still only 30% (hospital-based studies), so there is no dominant single gene.

8.2. The genes involved have not all been defined but studies have confirmed the importance of the HLA (immune response) genes. Prevalence in populations, families and twins has led to the conclusion that rheumatoid arthritis is a polygenic disease, with important non-inherited factors.

8.3. A relationship between **ethnicity** and prevalence in some populations offers further confirmation of a genetic factor e.g. the high prevalence in some Amerindian tribes with high frequency of HLA II antigens. Conversely, there is a low prevalence in sub-Saharan Africans, but urbanised black South Africans suffer similar prevalence to the white population, strong suggesting an **environmental** effect.

8.4. **Hormones**. Up to the menopause, rheumatoid arthritis is far more common in females than males. The contraceptive pill appears to exert a protective influence. These observations led to the suggestion that sex hormones are important in the aetiology.

8.5. **Infective agents**. The idea that infection may be a causal factor is not new. Rheumatoid arthritis has many features in common with reactive arthritis, a condition clearly related to infection. Epstein--Barr virus, rubella, parvovirus, mycoplasmae, atypical mycobacteria and B proteus have all been suspected but positive (ie reproducible) evidence that any of these organisms may play an aetiological role in rheumatoid arthritis is lacking.

8.6. Other aetiological factors. Infections, vaccinations, physical trauma and psychosocial stress have been suggested as triggering effects. Diet has also been suggested as an influence. There is however no objective evidence that any of these factors affect the cause or course of the disease. The onset has a distinct seasonal variation, starting twice as commonly in winter, but the reason for this is unknown. There is no evidence that this is due to a specific process such as precipitation of vasculitis, rather than a greater sensitivity to joint symptoms in cold weather.

8.7. In contrast to many other bone and joint diseases including gout, osteoarthritis and ankylosing spondylitis, there is a lack of archaeological evidence for antiquity of rheumatoid arthritis, leading to speculation that it is a relatively modern disease, perhaps triggered by an environmental factor.

8.8. Autoimmunity.

8.8.1. Rheumatoid arthritis is now thought to be an autoimmune disease. This follows the discovery of the **rheumatoid factor**, an IgM substance found in the sera of most rheumatoid patients. As immunology has advanced, it has become clear that the situation is complex. Some patients with classic clinical features of rheumatoid disease do not have rheumatoid factor (this is called sero-negative arthritis). Also, the factor is sometimes found in chronic infections and connective tissue disorders clinically distinct from rheumatoid arthritis and even in 5% of the normal population.

8.8.2. The body's immune system provides an essential barrier to a large range of pathogenic organisms. Autoimmune disease occurs if the immune response becomes directed at the body itself rather than at foreign antigens, thereby causing damage to the body's tissues.

8.8.3. Most work on autoimmune disease and its mechanisms has been done on animals. Despite recent advances in the molecular biology of the immune response, the precise aetiology of autoimmune disease remains unknown. In humans, genetic factors are thought to play a part. This is supported by studies of familial aggregation of the conditions and high concordance in monozygotic twins. However, concordance is not complete (see 8.1 above) so genetic factors alone are insufficient for disease to develop.

8.8.4. General, non-genetic factors thought to act to produce disease in predisposed individuals include infection (viral and bacterial), drugs and toxins. However, positive identification of specific factors in the individual conditions and cases is very rare. Individuals with one autoimmune disease appear to be at risk of other autoimmune conditions. The further conditions do not arise as a consequence of the first - the common factor is the genetic predisposition.

9. There is no evidence that the disease has any causal relationship to climate, latitude, metabolism, trauma, physical or mental stress, endocrine (eg thyroid, parathyroid, pancreas, adrenal) disorder, occupation factors (eg heavy work or exposure to chemicals) or cold and damp. However, in the established case, it is possible that some of these factors may influence the symptoms.

10. The effect of rheumatoid on mortality is probably underestimated. Actuarial studies demonstrate that life expectancy is reduced in all but the mildest forms of the disease. The 5-year survival rate of patients with extra-articular manifestations is less than 60%, and is particularly bad for those with pulmonary fibrosis, pericarditis, eye involvement and vasculitis.

CONCLUSION

11. **Rheumatoid arthritis** is a systemic disease which affects predominantly the locomotor system, although other systems are commonly involved. Its aetiology is unknown. It is thought that the condition results from the interaction of external factors in a predisposed individual, possibly through an autoimmune mechanism. Infective agents and sex hormones may act as inciting factors. Climatic factors, trauma and stress do not cause the condition.

12. It is not clear whether rheumatoid arthritis is a single disease, with all cases having the same aetiology, or a syndrome with a range of aetiological factors initiating the same pathogenetic mechanism and so producing a similar group of features.

REFERENCES

Cardoe N. In: Medical Selection of Life Risks. 3rd Ed. 1992. New York. Stockton Press. p807.

Jayson M I V, Grennan D M. Clinical Features of Rheumatoid Arthritis. In: Weatherall D J, Ledingham J G G and Warrell D A (Eds). Oxford Textbook of Medicine. 2nd Ed. 1987. Oxford. Oxford University Press. p16.3-16.11.

Maini R N, Feldman M. In: Oxford Textbook of Rheumatology. 2nd Ed. 1998. p984-985.

Panayi G S, Chapel H M. Immunopathology of Rheumatoid Arthritis. In: Weatherall D J, Ledingham J G G and Warrell D A (Eds). Oxford Textbook of Medicine. 2nd Ed. 1987. Oxford. Oxford University Press. p16.1-16.2.

Woo P. Molecular genetics and its relevance in rheumatology. In: Oxford Textbook of Rheumatology. 2nd Ed. 1998. Section 2.1.

Wordsworth B P. In: Weatherall D J, Ledingham J G G and Warrell D A (Eds). Oxford Textbook of Medicine. 3rd Ed. 1996. p2953 et seq.

Wordsworth B. P, et-al. In: Oxford Textbook of Rheumatology. 2nd Ed. 1998. p553.

October 1999