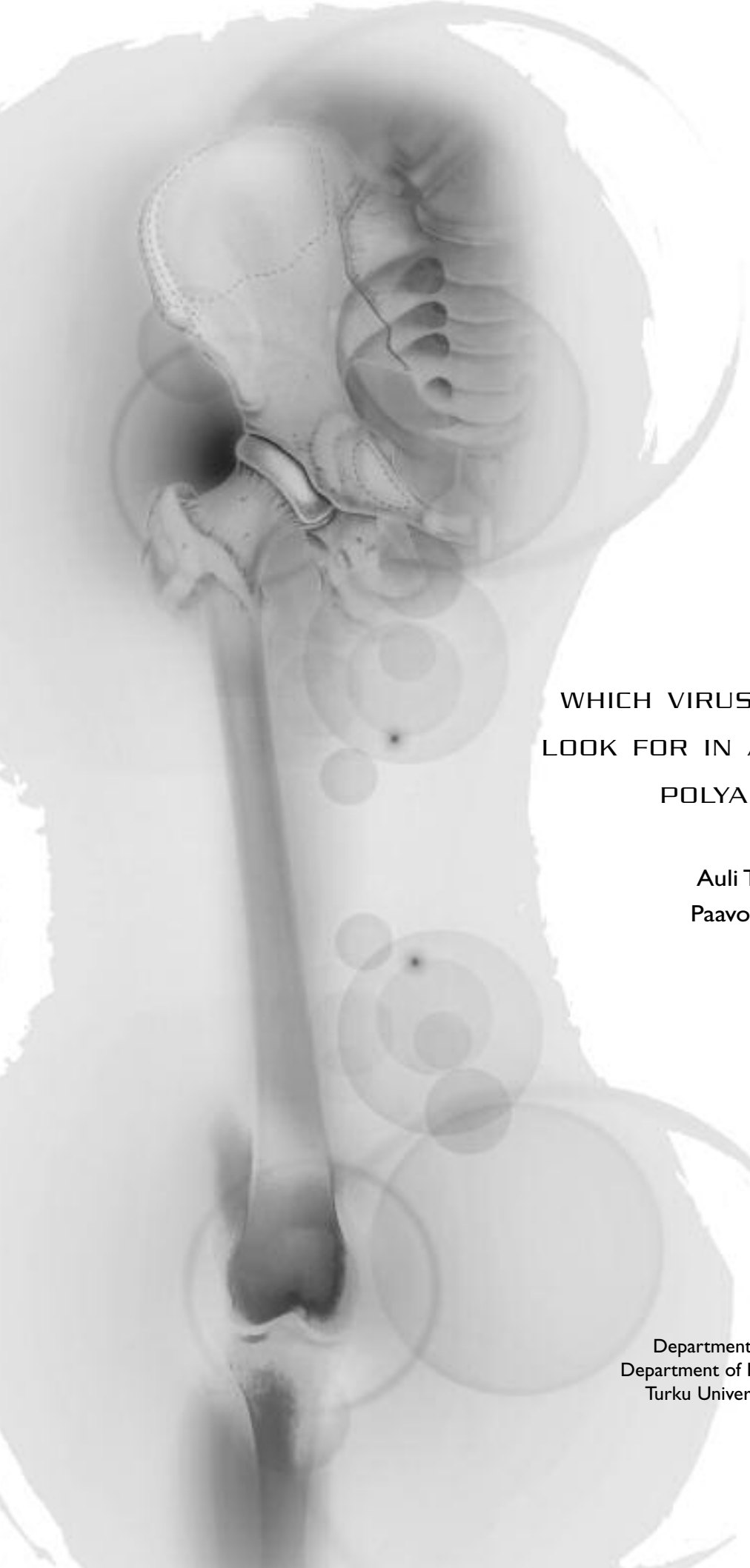

WHICH VIRUSES SHOULD WE LOOK FOR IN A RECENT ONSET POLYARTHRITIS

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ABSTRACT

This review is concentrated on specifically diagnosable viral diseases causing recent onset polyarthritis. A suspicion of viral etiology of arthritis should arise when there are symptoms of infection such as fever, skin manifestations, neurologic signs, or when several cases are occurring at the same time, suggesting an outbreak. In addition to the history and clinical examination, serology is a key element in the diagnosis. Some of these infections are known to occur at certain geographic areas, and the local clinicians are aware of this possibility. HIV and HCV infections occur worldwide, and they should be kept in mind when treating patients with recent-onset arthritis.

Keywords: Arthralgia; Arthritis; Etiology; Infection

RESUMO

Esta revisão analisa especificamente infecções virais diagnosticáveis causadoras de poliartrites agudas. A suspeita de uma etiologia viral numa artrite deve ser colocada quando surgem sintomas de infecção como febre, manifestações cutâneas, sinais neurológicos ou quando vários casos ocorrem ao mesmo tempo, sugerindo um surto infeccioso. Para além da história clínica e do exame objectivo a serologia é um elemento chave no diagnóstico. Algumas destas infecções ocorrem em determinadas áreas geográficas e os clínicos locais estão atentos a esta possibilidade. As infecções pelo HIV e HCV ocorrem em qualquer região geográfica e devem ser tidas em conta na abordagem de um doentes com uma artrite de início recente.

Palavras-Chave: Artralgia; Artrite; Etiologia; Infecção.

WHICH VIRUSES SHOULD WE LOOK FOR IN A RECENT ONSET POLYARTHRITIS

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It is a common experience by almost everyone that flu-like syndromes are quite often accompanied by arthralgia or even temporary mild arthritis. In this review we will concentrate on specifically diagnosable viral diseases causing recent onset polyarthritis. The role of viruses in the etiopathogenesis of chronic polyarthritis has recently been dealt with elsewhere[1].

A great global variation is observed in the viral causes of acute arthritis, for reasons related to epidemiology, climate and human sociology. Unlike bacterially induced arthritides, it is not possible to divide viral arthritides into hematogenous and reactive types. In fact, pure arthritis of viral origin, without involvement of any other tissues, has not been clearly documented. One must realise that the diagnosis of viral arthritis is always based on diagnosing a more or less generalised viral disease. On the other hand, demonstration of a virus in the synovial tissue alone does not necessarily indicate a viral arthritis, since so called innocent microbial bystanders are present in the human circulation and also end up in the synovial tissue.

The pathogenesis of viral arthritis may base on direct infection of synovial cells, formation of immune complexes or other mechanisms. Viral diseases that are accompanied by the development of arthritis can be divided into those in which the arthritis is common and those in which the arthritis occurs only rarely (Table I). For classification and more detailed description of viruses the reader is referred to textbooks[2-4].

Alphaviruses

Arboviruses, i.e. viruses spread by arthropod vectors include a group called alphaviruses. Several of them are pathogenic causing human infections often accompanied by arthritis (Table I). Typical for arboviruses is that they are transmitted to their vertebrate hosts mostly by mosquitoes. Their transmission cycles are complex, and several factors including the virus, the vector, and the host, or environmental variations may contribute to their geographic distribution. The viruses may multiply as well in the arthropod as in the vertebrate host[5-8]. They are able to persist in the environment for a long period in desiccation-resistant mosquito eggs, and therefore a rapid outbreak may occur when conditions become suitable. Regarding the vertebrate hosts, marsupials such as the Western grey kangaroo, wallabies or euros (*Macropus rotundus)* carry the Ross River virus. Migratory birds serve as hosts for several other alphaviruses, and obviously transport the viruses over long distances, contributing to their spread. It is thus understandable that the epidemiologic behaviour of the alphaviruses is quite capricious and their occurrence geographically restricted. An interesting example is O'nyong-nyong that caused in 1959 a vast epidemic in Africa, with more than 2 million cases reported in east Africa alone. Serologic evidence of exposure to the virus continued in Africa until the late 1960's, after which the transmission decreased and disappeared altogether. Then, in July 1996, the disease reappeared in southern Uganda after an absence of 30 years[9]. Regarding Ross River virus causing epidemic polyarthritis, a marked increase in its presence has been reported from Queensland, Australia[8].

One group of the alphaviruses, called Sindbis and Sindbis-related viruses, are geographically widely distributed, and the diseases caused by them seem to be more spread than earlier thoug[ht10,] 11. Sindbis virus was first isolated from mosquitoes in the village of Sindbis in Egypt in 1953. So far, in addition to Africa, it has been isolated also in Australia, Asia and Europe. Three closely related but not identical Sindbis-related viruses are known. Clinical cases

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Table I. Viral Diseases Accompanied by Acute Onset Arthritis

Virus	Virus present in joint*	Geographic occurrence+
Often accompanied by arthritis		
Alphaviruses		
Chikungunya		Africa, South East Asia
Mayaro		South America (Trinidad, Surinam, Brazil, Colombia, Bolivia)
O'nyong-nyong		Africa (Uganda, Kenya, Tanzania, Malawi, Senegal)
Igbo-ora		Ivory Coast
Ross River		Australia, New Guinea, Fiji, The Solomon Islands, American Samoa, South Pacific Islands
Barmah Forest		Australia
Sindbis		Africa, Australia, Asia, Europe
Sindbis-related		
Ockelbo		Sweden, Norway
Pogosta		Finland
Karelian fever		Russian Karelia
Hepatitis B virus		
Hepatitis C virus		
Parvovirus B19	Yes	
Rubella	Yes	
Seldom accompanied by arthritis		
Mumps		
Chickenpox	Yes	
Adenovirus		
Enteroviruses		
Echoviruses		
Coxsackieviruses		
Hepatitis A virus		
Herpes viruses		
Herpes simplex	Yes	
Varicella zoster	Yes	
Epstein-Barr virus	Yes	
Cytomegalovirus	Yes	
Retroviruses		
Human immunodeficiency virus (HIV)		
Human T-lymphocyte leukaemia virus (HTLV)-1		

*Demonstrated by culture, antigen detection or polymerase chain reaction in synovium/synovial fluid cells.
+When not global.

due to them have been reported in the northern, but not in central or southern Europe[12-14]. According to the location the diseases have been called Ockelbo disease in Sweden, Pogosta disease in Finland, and Karelian fever in the Russian Karelia.

The clinical symptoms caused by alphaviruses

vary considerably. Mostly the infection is of short duration and the prognosis is good, although several studies indicate that they may also give rise to chronic and prolonged symptoms, including arthralgia and arthritis. The general symptoms appear after an incubation time of 2 to 10 days. In addition to arthritis or arthralgia they may be fever, rash, headache and other central nervous symptoms. Chikungunya, Mayaro and O'nyong-nyong viruses also often cause hemorrhagic phenomena such as petechiae, purpura, epistaxis, and melaena[11]. In Ross River virus infections glomerulonephritis, and in Ross River and O'nyong-nyong infections lymphadenopathy has been described. Joint symptoms may be mild but also quite incapacitating in the acute phase of the disease. The names Chikungunya, O'nyong-nyong and Igbo-Ora have the meaning "weakening of the joints", "that which bends up", and "the disease that bends your wings", respectively.

The diseases caused by Sindbis-related viruses in northern Europe are most often seen in late summer or early fall, when people go to the woods to pick berries or collect mushrooms, and there are plenty of mosquitoes around[15, 16]. The main clinical symptoms are related to the joints, but rash, fever and headache are commonly seen. The disease can apparently pass subclinically.

The mechanism by which alphaviruses cause arthritis is unknown. It is known that Ross River virus can infect human synovial cells[15, 17, 18]. Although some alphaviruses have been isolated from human blood and skin, none have been isolated from the joints[11]. The diagnosis of alphavirus infection as cause of arthritis is based on the clinical picture. During the early phase virus isolation or demonstration of it by polymerase chain reaction (PCR) is possible, but thereafter the cornerstone for diagnostics is serology. It appears that in northern Europe especially during the late summer or early fall it is advisable to search for antibodies against Sindbis-related viruses, when a previously healthy person develops arthralgia or arthritis. The same certainly also holds true for Ross River virus infection in Australia. Regarding the other alphaviruses known to cause arthritic symptoms, a definite recommendation is more difficult to give.

Hepatitis viruses

Hepatitis A apparently gives rise to arthritis only rarely[19]. In contrast, both hepatitis B and C infections may occasionally give rise to extrahepatic manifestations, which also include arthritis and arthralgia. It is estimated that worldwide 350 million people are chronic hepatitis B virus (HBV) carriers, and chronic hepatitis C virus (HCV) infection affects 170 million individuals. The prevalence of these infections varies widely at different geographical locations, but they have to be kept in mind all over the world[20].

HBV is transmitted by sexual and parenteral route. The incubation period is usually 45 to 120 days. The arthritis is mediated by immune complexes composed of HBV surface antigens and corresponding antibodies. It is mostly sudden in onset, and it may be severe. Typically it is symmetric with simultaneous involvement of several joints at onset. It may also be migratory. The clinical picture may resemble that of rheumatoid arthritis. Arthritis and urticaria may precede jaundice by days to weeks and may persist even after jaundice has developed. However, most commonly the arthritis is limited to the pre-icteric period. In cases of chronic active hepatitis, the patient may have recurrent polyarthralgia or polyarthritis[21]. For the diagnosis, demonstration of HBV surface antigen in the serum is essential. There are numerous reports of arthritis occurring after HBV vaccination, apparently also mediated by immune complexes[22,23].

Of the three hepatitis viruses, HCV is the one most often associated with various autoimmune disorders[24]. Its transmission is mainly related to contact with blood and blood products. Sexual transmission has been reported but the frequency with which it occurs remains controversial[20]. It is lymphotropic as well as hepatotrophic, and can thus infect peripheral lymphocytes, lymphoid tissue and bone marrow. This ability contributes to the development of extrahepatic manifestations, which include among others fatigue, myalgia, pruritus and sicca syndrome. Of these extrahepatic manifestations, arthropathy is displayed up to 20% of infected patients[25, 26]. In a prospective study of 321 patients chronically infected with HCV rheumatologic symptoms were seen frequently, and 19% of patients suffered of arthralgia[27]. In this material frank arthritis was rare. According to Masuko-Hongo et al.[26] the arthritis involves multiple small joints, usually symmetrically, with morning stiffness and positive rheumatoid factor, thus strongly resembling rheumatoid arthritis. In contrast to classical rheumatoid arthritis, however, HCV-asso-

ciated arthropathy is non-deforming or non-bone--erosive and is free from subcutaneous nodules. Further, only half of the patients show elevated ESR. These features are useful for differentiation of the two categories of disease. The authors point out that in patients with rheumatoid arthritis--like symptoms, HCV infection should be screened for.

Parvovirus

Parvovirus B19 (B19) is the only known human pathogenic parvovirus. Infection may occur totally asymptomatic or with mild non-specific symptoms. B19 causes several clinical manifestations, the commonest being erythema infectiosum, the fifth rash disease of children. There is published evidence of B19 infection in association with congenital and acquired immunodeficiency, in fetuses of non-immune women experiencing B19 infection[28], and in association with certain vasculitides[29,30] and arthropathies[31,32]. Sixty to 80 % of infected adults suffer of joint symptoms, usually lasting a few weeks. Arthralgia occurs mainly in the wrist, hand, knee and ankles, usually symmetrically. Several cases of more or less chronic polyarthritis have been described, some of them meeting American College of Rheumatology criteria for rheumatoid arthritis, even with erosions and development of rheumatoid factor[33-37]. No clear association to the occurrence of rheumatoid arthritis susceptibility epitope has been observed[38-40]. The virus DNA is often demonstrable in the affected joints[35,36,41-44]. All these findings could be interpreted to indicate that parvovirus B19 might be a real etiological factor in a small proportion of rheumatoid arthritis cases. However, the viral DNA occurs also in joint tissues of trauma patients and in other control samples[43-46], and the virus has a tendency for persistence in a good proportion of the infected patients[47]. Altogether, a general view of today is that parvovirus B19 is not a cause of rheumatoid arthritis[36,44,48-51]. An outbreak of parvovirus arthropathy, mostly representing a migratory arthritis, has also been described[52].

Parvovirus laboratory diagnostics is based primarily on serology. Because parvoviruses are difficult to culture in vivo, lack of native antigen has limited the availability of the test. Antigen purified from viraemic human sera, synthetic peptides and recombinant antigens have been used[53]. Methods based on the detection of B19 DNA have been described in several reports. As a routine clinical test, dot-blot hybridisation and DNA amplification by PCR have been reported to be useful[34, 54, 55].

Rubella

In the rubella infection arthralgias are common, occurring before or after the rash, particularly in women. A more severe symmetric or migratory arthritis may also develop, but usually subsides in a few days or weeks, even though cases with a more persisting polyarthritis have been described. Use of live attenuated rubella vaccines may also result in joint symptoms of short duration, including recent onset polyarthritis[56].

Retroviruses

An increasing number of patients with human immunodeficiency virus (HIV) infection and concomitant rheumatic disorders have been reported[57,58]. These range from mild arthralgias to severe diseases. It is unclear what role the HIV itself or the immunodeficiency plays in the pathogenesis of arthritis. The arthralgias are generally intermittent, mild and polyarticular. They are mostly observed in the latest stages of HIV infection. A more severe form is asymmetric oligoarthritis resolving in a few weeks[59-61]. Also patients with exquisite pain in the knees and ankles lasting only a few hours or days have been described[62]. In contrast to the polyarthritis associated with HIV infection, the arthritis occurring in the human T-lymphocyte leukaemia virus-1 (HTLV-1) infected patients is oligoarthritis and mostly chronic by the nature[63].

Others

Other viral infections which sometimes, even though quite unusually, are accompanied by acute onset polyarthritis include those caused by the following: mumps, chickenpox, adenoviruses, enteroviruses (echo- and coxsackieviruses) and herpesviruses (herpes simplex, varicella zoster, Epstein-Barr virus and cytomegalovirus)[21,64-66]. A few cases of chickenpox associated with septic arthritis have been described[67,68].

Concluding remarks

A suspicion of viral etiology of arthritis should arise when there are symptoms of infection such as fever, skin manifestations, neurologic signs, or when several cases are occurring at the same time, suggesting an outbreak. Some of these infections are known to occur at certain geographic areas, and the local clinicians are aware of this possibility. In addition to the history and clinical examination, serology is a key element in the diagnosis. HIV and HCV infections occur worldwide, and they should be kept in mind when treating patients with recent-onset arthritis. This is important to prevent further spread of the infection, but also to install proper therapy. In HCV associated arthropathy, there is some evidence that anti-virus treatment with interferon-α may lead to substantial improvement [26]. In HIV-infections, the need of antiviral agents is obvious.

For the patient with acute arthritis the question regarding the prognosis is of great importance. Many fear that they will develop a chronic, slowly disabling condition. In most instances the prognosis of viral induced arthritis is better than that of rheumatoid arthritis, as pointed out above. Therefore good clinical work-up includes search for a possibility of viral etiology.

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