"Non-Infectious" Syndromes Associated With Infectious Agents

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Summary

Over the past two decades there has been numerous new associations between chronic diseases traditionally considered non-infectious with infectious agents. This list of diseases include peptic ulcer, coronary heart disease, neuropsychiatric disorders, haematological disorders and malignancies. These associations have been made possible through improvements in diagnostic tests based on molecular biology techniques. The discovery of these associations is important as it opens up exciting opportunities for the prevention and treatment of many diseases hitherto considered incurable.

Key Words: Infectious agents, Infectious diseases, Chronic diseases, Gastroduodenal disease, Coronary heart disease, Neuropsychiatric disorders, Cancer

Introduction

The association between infectious agents and "non-infectious manifestations" has long been recognised. One of the best examples of an infection with protean manifestations is syphilis. Syphilis has been described as the "big imitator" in the early 20th century. Over the past two decades many more such associations between infectious agents and so-called "non-infectious" chronic syndromes have been discovered. This has been made possible largely because of progress in laboratory techniques. These new laboratory techniques which employ molecular biology methods are highly sensitive and specific; enabling scientists to establish the presence of infectious agents which had previously escaped detection with the older less sensitive techniques.

Gastrointestinal diseases

Helicobacter and gastroduodenal disease

One of the most remarkable discoveries in the past two decades has been the identification of *Helicobacter pylori* as the causative agent in certain gastroduodenal diseases. This was due to the pioneering work by Marshall and Warren in the 1980s[1]. *Helicobacter pylori* is a curved gram-negative bacterium which is now recognised to be the causative agent for duodenal ulcer, gastric ulcer, gastric carcinoma and gastric lymphoma[2,3]. The pathogenesis of helicobacter disease is the result of various virulence factors elaborated by the bacterium[4]. *H. pylori* is a prolific producer of the enzyme urease. Urease catalyses the breakdown of urea to ammonia and carbon dioxide. The ammonia neutralises the hydrochloric acid in the stomach and enables the bacterium to survive in the hostile acid environment. Ammonia is also deleterious to gastric epithelium. The bacterium produces a cytotoxin which injures the epithelial cells of the stomach and duodenum. It has surface membrane proteins which are cytokine stimulating, thus provoking an inflammatory response and causing further damage.

Two major pathogenetic mechanisms of helicobacter disease has been recognised. The first is in a situation of increased gastric acid which leads to gastric metaplasia

and ulcer formation. The other is against a background of decreased acidity where chronic infection results in chronic atrophic gastritis and gastric cancer. A meta-analysis of studies linking *H. pylori* infection and gastric cancer concluded that the risk of gastric cancer in those with *H. pylori* infection may be as great as nine times that of their uninfected counterparts[5]. Why certain individuals develop ulcers and others have chronic gastritis is not known for certain. It is likely that bacterial virulence factors in combination with host factors, such as differences in immune and reparative responses may determine the ultimate outcome of the infection.

Other helicobacter associated diseases

Helicobacter infection has also been associated with coronary artery disease. The association which is based on serological surveys is rather weak and may be accounted for by confounding factors[6]. Another disease associated with *H. pylori* is Menetrier's disease; a rare protein-losing hypertrophic gastritis[7]. This condition has been shown to respond to antibiotics which are active against helicobacter[8].

Other gastrointestinal diseases

Whipple's disease is a condition which has been recognised for nearly a century. However the aetiology was unknown until the early 1990s when the presence of an infectious agent was demonstrated in diseased tissues. The detection of the agent was made possible by a polymerase chain reaction (PCR) technique which enabled the scientists to amplify the ribosomal RNA of the pathogen in diseased tissues obtained from five patients. By sequencing the amplified products it was possible to classify the organism even though the agent had not been previously cultured. Based on the nucleic acid sequence of the organism, it was classed as an actinomycete and was given the taxonomic name, *Trophyrema whipelli*[9]. More recently *Trophyrema whipelli* has been cultured using IL-4 deactivated monocytes[10]. Crohn's disease has been associated with *Mycobacterium pseudotuberculosis* but recent PCR work does not support an aetiological role[11].

Coronary Heart Disease

Chlamydia pneumoniae

There is now increasing evidence for an association between coronary heart disease and *Chlamydia pneumoniae* infection. *C. pneumoniae* or TWAR (Taiwan acute respiratory agent) is a bacterial organism which can only grow intracellularly. It was first described in Taiwan as a cause of acute respiratory infection[12]. The association between *C. pneumoniae* and coronary heart disease has been based on several lines of evidence.

Serological surveys have shown that patients with coronary heart disease are more likely to have antibodies to *C. pneumoniae*. Wong *et al* recently undertook a systematic review of the serological evidence linking *C. pneumoniae* infection and coronary heart disease[13]. They showed that 21 of 27 studies have reported some sort of positive serological association. However, although all studies measured IgG, only three prospective and 15 cross sectional studies measured IgA. Of the cross sectional studies, five found an association with both immunoglobulins, three with IgG alone, and two with IgA alone. Five studies found no association with either immunoglobulin, although three of these did show an association with circulating chlamydial immune complexes. They concluded that based on the serological evidence it is difficult to establish that chronic rather than past *C pneumoniae* infection is associated with atherosclerosis.

Using sensitive methods like PCR, immunocytochemistry and electron microscopy the agent has been detected in diseased tissues. Shor *et al* demonstrated the presence of chlamydial-like organisms in the coronary arterial fatty streaks and atheromatous plaques in 7 autopsy cases. The organisms were observed ultrastructurally in the lipid-rich core area of fibrolipid plaques and in intimal smooth-muscle cells. In 5 cases, immunoperoxidase staining showed positive reactions to *Chlamydia* genus- and *C. pneumoniae* species-specific monoclonal antibodies[14]. In another study, 38 fresh tissue specimens from patients with coronary artery lesions were tested for *C. pneumoniae* using polymerase chain reaction (PCR) and immunocytochemical stain (ICC)[15]. In 20 of 38 specimens the tests were positive by either one or both methods. The organisms were localized to macrophages. Ultrastructural evidence of the organism was found in 2 specimens by transmission electron microscopy. These specimens were also positive by both ICC and PCR.

C. pneumoniae has also been successfully cultured from atherosclerotic plaques in one patient with severe coronary artery disease[16]. The organism was found in the

atheromas of this patient by PCR assay, immunocytochemistry, electron microscopy, and in situ hybridization. In another report the organism was cultured from a carotid endarterectomy specimen[17]. In Malaysia, evidence of *C. pneumoniae* infection has been found in patients with mycocardial infarction and coronary heart disease using a PCR detection technique[18].

There has also been animal studies where infection of laboratory animals with *C. pneumoniae* led to the formation of atheromatous plaques. In one study, rabbits were infected intranasally with *C. pneumoniae* resulting in the animals showing inflammatory changes in vessel walls. The changes consisted of intimal thickening or fibroid plaques which resembled atherosclerosis[19]. In another animal study, weekly treatment with azithromycin after infectious exposure of the animals prevented accelerated intimal thickening[20].

Finally there has been a few treatment studies where treatment with anti-chlamydial antibiotics have been associated with a decreased rate of adverse cardiovascular events following myocardial infarction (MI). In one randomised, placebo-controlled clinical trial it was found that treatment with azithromycin reduced the risk of post-MI cardiovascular events in male patients who had high titres of anti-chlamydial antibodies (titre of > or = 1/64). The risk of such events in the azithromycin-treated patients was similar to those who were antibody negative. In this study it was also shown that patients with high antibody titres to *C. pneumoniae* had a four-fold increased risk of post-MI adverse cardiovascular events compared to those who were antibody-negative[21]. In another trial patients with non-Q wave acute coronary syndromes were randomised to receive roxithromycin (another macrolide) or placebo. It was found that roxithromycin reduced the risk of death or re-infarction for at least six months after initial treatment[22]. However a recent large randomised, placebo-controlled trial of azithromycin (the ACADEMIC study) on 302 coronary heart disease patients positive for *C pneumoniae* antibodies did not show any differences in antibody titers or clinical events between the treated and control groups. There was however evidence in improvement of four markers of inflammation after 6 months treatment with azithromycin[23]. Longer-term and larger studies of anti-chlamydial therapy are required to establish the role of antimicrobial treatment in coronary heart disease.

It is postulated that following *C. pneumoniae* infection of the lungs the agent gain access to the coronary arteries via the blood stream where it then infects previously damaged intimal sites. The multiplication of chlamydia in these sites is accompanied by inflammation and subsequent plaque formation. Exposure of macrophages to *C. pneumoniae* followed by low-density lipoprotein (LDL) caused a marked increase in the number of foam cells, the hallmark of early atherosclerosis[24]. *C. pneumoniae* produces a heat-shock protein (HSP-60). This heat shock protein is produced in large quantities in chronic chlamydial infections. This protein can activate human vascular cell functions that are relevant to atherogenesis and lesional complications[25].

The association with coronary heart disease though strong has by no means established an aetiological role for *C. pneumoniae*. There are potential confounding factors which have to be taken into account. Chronic respiratory infection and coronary heart disease are more common in the same categories of pateints i.e. smokers, elderly and the lower socioeconomic groups. Furthermore patients with coronary heart disease are more susceptible to respiratory infections. It has also not been established whether chlamydial infection preceded or followed development of the atherosclerosis. Therefore a cause-effect relationship remains unproven and more clinical studies will have to be conducted[26].

Neuro-degenerative disorders

Prion diseases

Prions are proteinaceous infectious agents[27]. They are unique as infectious agents as they do not have any nucleic acid but are merely made up of protein. Prions are known to cause various neuro-degenerative disorders referred to as transmissable spongiform encephalopathies (TSE) in both animals and man. In man the infections include kuru, Cruetzfeldt-Jakob disease (CJD) and new variant Cruetzfeldt-Jakob disease (NV-CJD), Gerstmann-Straussler syndrome and Fatal Familial Insomnia[28].

These are all very rare diseases. The incidence of sporadic CJD is only about 1 per million per year. However NV-CJD had recently received a lot of attention because of its association with the consumption of bovine products from cattle afflicted with bovine spongiform encephalospathy or mad cow

disease. These infections are characterised by loss of motor control, dementia, paralysis, wasting and inevitable death usually following pneumonia.

Prions infect humans in two ways. The first is through acquired infection where the infectious agent is acquired either through diet or medical procedures. Kuru was transmitted through cannibalism practised by some tribes in the highlands of New Guinea and the disease has been eradicated with the cessation of cannibalism. Cases of CJD have been reported following corneal transplantation and injection of growth hormone derived from human pituitaries. Prion diseases can also be transmitted in an autosomal dominant fashion. Thus prion diseases are both infectious and hereditary.

The pathogenesis of prion diseases is still unclear but it involves the replacement of a normal cellular protein, $PRP^{(C)}$, by a modified form referred to as $PRP^{(Sc)}$. The normal cellular protein is found predominantly on the surface of neurones and believed to be essential in synaptic function. The normal protein is protease sensitive while the modified prion protein is protease resistant. When $PRP^{(Sc)}$ (the prion) is introduced into a normal cell it somehow causes a post-translational conformational change of the normal $PRP^{(C)}$ into $PRP^{(Sc)}$.

Slow virus infections

Several conventional viruses also cause degenerative neurological disorders[29]. These diseases are characterised by a long asymptomatic incubation period of months to years and overt clinical illness of an equally prolonged duration. Progressive multifocal leucoencephalopathy (PML) is caused by a papovavirus (JC virus)[30]. PML is a progressive demyelinating condition that occurs in immunocompromised patients. It has been seen in patients with leukaemias, Hodgkin's disease and HIV infection. PML is invariably fatal. Subacute sclerosing panencephalitis is due to the measles virus and a similar condition, rubella panencephalitis is caused by the rubella virus.

Tropical spastic paraparesis

Tropical spastic paraparesis (TSP) or HTLV-1 associated myelopathy (HAM) is a neurological disorder found in East Asia and the Caribbean[31]. The causative agent is Human T-cell Lymphotrophic Virus (HTLV-1)[32].

The incidence of the condition is between 5.1-128/100,000 population in endemic areas. The average age of diagnosis is 40 years. Clinical features of HAM/TSP include muscle weakness in the legs, hyperreflexia, clonus, extensor plantar responses, sensory disturbances, urinary incontinence, impotence, and low back pain. Laboratory diagnosis includes detecting the presence of the virus and its antibodies in cerebrospinal fluid, brain and spinal cord tissues.

Guillain Barre syndrome

With the increasing rarity of poliomyelitis the most common cause of flaccid paralysis today is the Guillain Barre syndrome. This is an auto immune disorder triggered off by an antecedent infection. The most common antecedent event is *Campylobacter* infection accounting for about 30% of Guillain Barre syndrome cases in the United States. The mechanism of disease in *Campylobacter* associated Guillain Barre syndrome is the molecular mimicry between ganglioside moieties in the lipopolysaccharide of *Campylobacter* and the glycolipids and myelin proteins of nerve tissue[33].

Other CNS diseases

Multiple sclerosis has been associated with Human herpes virus-6 (HHV-6) infection, a retrovirus named the MS associated retrovirus and the Borna Disease Virus[34-36]. Bell palsy has been shown to be associated with Herpes simplex virus-1 (HSV-1). The viral genome has been detected in endoneural fluid of the facial nerve and the posterior auricular muscle of Bell palsy patients[37]. The use of acyclovir in the treatment of Bell palsy remains controversial but it has been shown that Bell palsy patients who received prednisone alone had lower facial function scores and were three times more likely to have an unsatisfactory outcome compared with those given a prednisone-acyclovir combination[38].

Psychiatric disorders and infection

Borna Disease Virus

Borna Disease Virus (BDV) is a RNA virus of animals first identified in the 19th century. It owes its name to the town of Borna in Saxony, Germany, where a large number of horses died during an epidemic in 1885. BDV causes a fatal neurological disease of horses and sheep.

Recently it has been shown that patients with schizophrenia and depression or bipolar disorders are more likely to have antibodies to BDV. In one study the seroprevalence rate was 9.6% among a group of neuropsychiatric patients compared to 1.4% in healthy controls[39].

BDV RNA has also been detected in post-mortem brains of patients with schizophrenia and bipolar disorders[40]. However much more work needs to be done to establish an aetiological role for the virus.

HIV dementia

HIV-associated dementia can also present with a variety of neuropsychiatric symptoms. These neurocognitive deficits can severely impair the patient's ability to perform daily activities. The symptoms include impaired concentration, motor speed, learning ability and speed of information processing.

PANDAS

Streptococcal infection in children can be followed by various neuropsychiatric disorders including tics and behavioral disturbances. Sydenham's chorea has long been recognised as a feature of rheumatic fever. Other neuropsychiatric disorders which have been described include emotional lability, motor hyperactivity, separation anxiety, Tourette's-like symptoms and obsessive-compulsive behavior. This syndrome has been termed paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection or PANDAS[41].

Extrahepatic manifestations of Hepatitis C

Hepatitis C is a blood-borne viral infection and a major cause of transfusion associated hepatitis. Although the primary manifestations of this viral infection are hepatic in nature, there are also numerous non-hepatic conditions which are associated with the infection[42]. Strong associations has been shown with essential mixed cryoglobulinaemia, porphyria cutanea tarda and membranoproliferative glomerulonephritis. Moderately strong associations are seen with Mooren corneal ulcer and autoimmune thyroiditis and weak associations have been described with Sjogren syndrome, lichen planus and idiopathic pulmonary fibrosis. Treatment with interferon has been reported to be beneficial in essential mixed cryoglobulinaemia[43].

Kawasaki disease

Kawasaki disease or the mucocutaneous lymph node syndrome is a disease of childhood characterised by fever, rash, conjunctivitis, lesions on the oral mucous membranes and cervical lymphadenopathy. A possible infectious aetiology has been postulated because of the observation that Kawasaki disease can occur in the form of seasonal outbreaks. There is some evidence that the disease may be due to the release of superantigens of toxins from pharyngeal and bowel flora into the blood stream. These superantigens activate T-cells in a non-specific manner thus resulting in the release of pro-inflammatory cytokines[44]. A retroviral role has also been postulated[45]. Shibata has also recently reported an association with *Corynebacterium* sp[46].

Renal disorders

Glomerulonephritis

Immune complex glomerulonephritis has been associated with a variety of infections including viral, bacterial and parasitic infections[47]. The viruses include Hepatitis A, B, C and G; parvovirus, Epstein-Barr virus, cytomegalovirus and varicella-zoster virus. Bacterial infections include infections due to Group A beta-haemolytic streptococcus, *Staphylococcus aureus, Mycoplasma pneumoniae* and *Coxiella burnetti*. Glomerulonephritis is also a feature of infective endocarditis.

Haemolytic-uraemic syndrome

The haemolytic uraemic syndrome (HUS) is a syndrome characterised by acute renal failure, microangiopathic haemolytic anaemia and thrombocytopaenia. HUS is most often caused by the release of verocytotoxin by certain bacteria[48]. The most common cause is *E. coli* O157 which causes bloody diarrhoea. However other infective agents have also been associated with HUS. They include non-O157 *E. coli, Citrobacter* sp and *Shigella dysenteriae* which can produce a similar toxin. HUS can also occur in infections due to *Streptococcus pneumoniae*[49], *Campylobacter*[50], *Aeromonas*[51], *Clostridium septicum*[52], parvovirus[53], HIV[54] and Epstein-Barr virus[55]. In the case of pneumococcal infections the pathogenesis is related to the neuraminidase enzyme produced by the organism. This enzyme causes the exposure of the T-cryptantigen (Thompsen-Friedenreich antigen) found on surfaces of red blood cells, platelets and glomerular capillary walls.

As most people possess a naturally occurring antibody against the cryptantigen, the ensuing antigen-antibody interaction leads to cellular damage[49].

Parvovirus B19

Parvovirus B19 is a DNA virus which was shown to be the cause of erythema infectiosum or the 5th disease[56]. In addition parvovirus B19 has been associated with several haematological disorders including aplastic crisis, hydrops foetalis and the haemophagocytic syndrome[57]. In the parvovirus B19 associated disorders, treatment with intravenous gamma-globulin may be beneficial. Recently parvovirus B19 has also been associated with giant cell arteritis[58].

Infection and cancer

Many infectious agents have been associated with malignancies. Hepatitis B and C infections are associated with hepatocellular cancer. The Epstein-Barr virus is associated with Burkitt's lymphoma, nasopharyngeal carcinoma and Hodgkin's lymphoma.

The papillomaviruses (HPV) has been linked to a variety of malignancies including carcinoma of the cervix, bladder cancer, oral cancers, oesophageal cancer and skin cancers[59]. The link between cervical cancer and their pre-malignant lesions with papillomaviruses is very strong, in particular with HPV types 16, 18, and a few others. Clinical trials are being conducted on HPV vaccines, directed particularly against HPV 16 and 18. If proven to be effective, these vaccines will have a major impact on the incidence of one of the most common malignancies in women.

Kaposi sarcoma is now known to be associated with Human Herpes Virus 8 (HHV-8)[60]. This virus is also associated with two other malignant conditions namely primary effusion body cavity-based lymphoma (PEL) and multicentric Castleman disease[61]. PEL is a recently recognized subtype of malignant lymphoma that manifests primarily as a malignant effusion. Both AIDS related and non-AIDS related PEL are found to be infected with HHV-8. A vast majority of the lymphomas also contain Epstein-Barr virus (EBV) and this is an example of a dual viral infection in a malignancy[62]. Multicentric Castleman disease is a systemic illness with disseminated lymphadenopathy and runs an aggressive and usually fatal course. It is associated with infectious complications and risk for malignant tumors, such as lymphoma or Kaposi sarcoma. It has also been described in association with HIV infection. The association with human herpesvirus-8 may help explain why non-HIV patients with Castleman disease have developed Kaposi sarcoma[63].

There has been only one report of a malignancy linked with a bacterial agent apart from *H. pylori*. *Mycoplasma* sp has been associated with ovarian cancer[64].

Conclusion

There are now numerous associations between infectious agents and syndromes which have classically been considered non-infectious in origin. Causal relationships are however more difficult to prove and will require additional epidemiological and clinical studies. In the future many more such relationships will be discovered as diagnostic tools become more sensitive and specific. Such new knowledge opens up exciting prospects for the prevention and treatment of conditions previously considered incurable.

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Questions For "Non-Infectious" Syndromes Associated With Infectious Agents

1. *Helicobacter pylori* is the cause of:
   A. gastric ulcer
   B. duodenal ulcer
   C. pernicious anaemia
   D. gastric lymphoma
   E. Menetrier's disease

2. Evidence of a link between *Chlamydia pneumoniae* and coronary heart disease (CHD) include:
   A. patients with CHD are more likely to have antibodies against *Chlamydia pneumoniae*
   B. *Chlamydia pneumoniae* has been detected in atheromatous tissue using PCR
   C. Macrolide antibiotics have been successful in the primary prevention of CHD
   D. *Chlamydia pneumoniae* have been cultured from atheromas
   E. Vaccination against *Chlamydia pneumoniae* prevents CHD

3. Prions are the cause of:
   A. Creutzfeldt -Jacob disease
   B. Koro
   C. Gertsmann-Straussler syndrome
   D. Progressive multifocal leucoencephalopathy
   E. Fatal Familial Insomnia

4. Extrahepatic manifestations of Hepatitis C infection include:
   A. adult T-cell lymphoma
   B. porphyria cutanea tarda
   C. essential miixed cryoglobulinaemia
   D. membranoproliferative glomerulonephritis
   E. haemolytic uraemic syndrome

5. Cancers associated with herpesviruses include :
   A. cancer of the cervix
   B. ovarian cancer
   C. Burkitt's lymphoma
   D. Kaposi sarcoma
   E. Primary effusion body cavity-based lymphoma