New hepatitis viruses beyond HCV

S. T. Lai
Department of Medicine and Geriatrics, Princess Margaret Hospital

Cloning of the hepatitis C virus (HCV) dramatically changed the approach for viral discovery. Instead of a tissue culture system, an observed particle, a serological assay or a means to measure viral replication, HCV was discovered by blind cloning, immunoscreening of expressed proteins and the detection of novel nucleic acid sequences. The above practice has become the paradigm for the search for new hepatitis viruses.

This article introduces readers to new hepatitis viruses beyond HCV, with the exception of the hepatitis E virus which is already a well-known enteric pathogen. A retrospective analysis of prospectively followed transfusion recipients in the NIH series[(1)] showed that 12% of non-A, non-B hepatitis cases were not related to HCV infection. Most of these non-A, B, C cases had asymptomatic infection and mild biochemical abnormalities, but more marked aminotransferase elevations were noted in some and roughly 20% appeared to develop chronic hepatitis. Lastly, up to 30% of cases of chronic hepatitis and cirrhosis have no known aetiology and are labelled as cryptogenic [(2)]. An argument could be made for the existence of at least one additional human hepatitis agent. Conversely, those cryptic cases can be due to missed HBV and HCV infection or non-infectious causes such as unrecognised drug toxicity.

The GB agent (after the patient's initials) was found in the 1950's and renewed investigation of the stored frozen serum by selective amplification and subtractive cloning characterized the virus in 1995 [(3)]. More than one GB agent was later detected and they were designated GBV-A, GBV-B and GBV-C. In 1996, another agent was identified by amplification strategy, which was proven to be a flaviviridae and was designated the hepatitis G virus (HGV)[(4)]. Subsequent sequence comparisons revealed that GBV-C and HGV were essentially the same agent. It was found in 2 - 4% of blood donors, readily transmitted by blood transfusion and could lead to persistent infection in recipients. However, the virus was found with equal frequency in patients who did or did not develop hepatitis and no consistent relationship was shown between the level of viraemia and the degree of liver damage. Furthermore, there is no evidence that the agent replicates in the liver. Despite extensive worldwide investigations over the past decade, GBV-C / HGV has not been shown to cause hepatitis or other known liver or non-liver diseases.

A new viral clone was discovered in patients with transfusion associated hepatitis in Japan in 1997[5]. The agent was designated TT virus (TTV) after the patient's initials. Further studies showed that it was a non-enveloped virus containing circular DNA and was closely related to circoviridae, a family of animal viruses not previously associated with human disease. Circoviridae can now be classified into at least 16 genotypes with a wide sequence divergence. Epidemiological studies have confirmed that TTV is a parenterally transmitted agent but proof that it replicates in the liver is still lacking. The initial study in Japan suggested a relationship of TTV to acute and chronic liver disease, but a subsequent study [6], showed no significant difference between the prevalence of TTV in patients with chronic liver disease and healthy controls. The rate of TTV infection was found to be similar among patients with various liver diseases and did not define the group with non-A - G hepatitis. Like that occurred in investigations with HGV, the prospective NIH series [7] also did not support a causal association between TTV infection and post-transfusion hepatitis.

In performing further phylogenetic analyses of TTV in Japan, two variants of TTV had been isolated in 1999[8]. The first was designated SANBAN which is quite distant from the prototype TTV and may represent a new TTV-like viral species. The second had been designated YONBAN which is also a distant variant of the TTV family. In additional studies from that laboratory [9] a new human virus resembling TTV was reported and was designated the TTV-like mini virus (TLMV). Though linked by common biophysical characteristics, the sequence difference between these agents are so great that they may have totally different clinical spectrums and disease associations.

A viral discovery programme by Diasorin Corporation found a novel agent designated SEN after the initials of the patient. The SEN virus (SEN-V), like TTV, proved to be a small, non-enveloped, singled-stranded DNA virus. It was not only widely divergent from TTV, but it represented a subfamily of very heterogeneous variants. As the TTV family expanded to include SANBAN, YONBAN and TLMV, it has become apparent that SEN-V is most closely related to SANBAN. There have been various studies on the clinical relevance of SEN-V and results of the NIH prospective study projected that no more than 6% of SEN-V infections were accompanied by biochemical evidence of hepatitis. In separate international studies, no association was shown between SENV infection and acute liver failure and chronic liver disease. The only clinical correlation so far is with acute transfusion-associated hepatitis[10].

In spite of confusing nomenclature and uncertain clinical relevance, it now seems firmly established that there is a newly discovered complex family of viruses capable of infecting human. This appears to be a super-family of relatively small, nonenveloped, single-stranded circular DNA viruses similar to previously described animal viruses designated circoviridae. However, the association of these agents with liver disease is uncertain. The vast majority of infected patients have no evidence of liver disease. Because the circoviridae are so diverse, the agents within this family may have different disease manifestations, making clinical investigations difficult. Definition of optimal primers, large-scale population testing, development of antibody assays and more rational reclassification and renaming of the agents will be the foci in future studies.

Reference

1. Alter H. J. et al. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. New Engl J Med 1989; 321:1494-500.
2. Alter H. J. et al. Non-A, non-B hepatitis unrelated to the hepatitis C virus (non-ABC). Sem Liv Dis 1995; 15:110-9.
3. Simons J. W. et al. Isolation of novel virus-like sequences associated with human hepatitis. Nature Med 1995; 15: 564 - 9.
4. Linnen J. et al. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent. Science 1996; 271: 505 - 8.
5. Nishizawa T. et al. A novel DNA virus (TTV) associated with elevated transaminase levels in post-transfusion hepatitis of unknown aetiology. Biochemical and Biophysical Research Communications 1997; 241:92-7.
6. Nauomov N. et al. Presence of a newly described human DNA virus (TTV) in patients with liver disease. Lancet 1998; 352: 195 - 7.
7. Matsumoto A. et al. Transfusion-associated TT virus infection and its relationship to liver disease. Hepatology 1999; 30:283-8.
8. Takahashi K. et al. Full or near full length nucleotide sequence of TT virus variants (Types SANBAN and YONBAN) and a TT virus-like mini vims. Intervirology 2000; 43:119-23.
9. Takahashi K. et al. Identification of a new human DNA virus (TTV-like mini virus, TLMV) intermediately related to TT virus and chicken anemia virus. Arch Virol 2000; 145: 979 - 93.
10. Umemura T. et al. SEN virus infection and its relationship to transfusion-associated hepatitis. Hepatology 2001; 33: 130311.

Smallpox

T. K. Ng, Department of Pathology,
Princess Margaret Hospital

History

Smallpox was once the most feared infectious disease that had devastated human civilisation. With a mortality rate of 30% and rapid transmission through the respiratory-route, it had decimated whole native population, thus altering the course of history. Only humans are susceptible to the infection. Survivors were left with disfiguring scars or blindness. In 1796 Edward Jenner laid the foundation for the eradication of smallpox after he showed that inoculation of cowpox could protect people from smallpox infection. In 1958, WHO launched a global programme to eradicate smallpox. In 1967, the programme was intensified. Using the strategy of surveillance and containment of the infected and their contacts by quarantine and vaccination, smallpox was controlled and the last naturally occurring case was detected in Somalia in 1977. In 1978, two laboratory acquired infections occurred in the UK. No new cases occurred since then and smallpox was officially declared eradicated in 1980. Only two high security laboratories in the USA and Russia still keep stock of the variola virus. However, it is uncertain whether other countries have clandestine stockpiles of the virus. Now that all routine civilian vaccination has been stopped and the vaccinia vaccine is in short supply, the world is once again vulnerable to outbreak. The recent spate of bio-terror attacks in the USA makes us realise that nothing is impossible and we should be prepared for the re-emergence of this virus.

Epidemiology and clinical features

Smallpox is caused by the variola virus, a member of Poxviridae which also includes vaccinia and monkeypox. It is transmitted mainly by respiratory droplets during face to face contact with the infected. The less common means of transmission are by contact with contaminated clothing and linen and rarely by aerosol spread. The incubation period is usually 12 to 14 days (range 1 to 17 days).

After a prodrome of fever, headache, backache and malaise for 2 to 3 days, the patient develops lesions in the mouth and a maculopapular rash which turns into deep-seated, firm vesiculopustules in a few days. Eight to 14 days after the onset of rash, scabs form which, after shedding, leave depigmented depressed scars due to destruction of pilosebaceous glands. The lesions are centrifugally distributed with the face and extremities more involved than the trunk. The patient is highly infectious in the first week of the rash when oral secretion is loaded with virus. The virus in the scabs is less infectious, presumably because they are bound in the fibrin matrix. Helpful points to distinguish smallpox from chickenpox are: in the latter, absence of prodromal fever, centripetal distribution of rash, less prominent involvement of the soles and palms, superficial lesions, lesions at different stages of maturation being present at the same time and permanent scarring is uncommon unless complicated by self-inflicted trauma or secondary bacterial infection of the skin and soft tissues. Monkeypox also closely mimics smallpox except for the early and prominent enlargement of the lymph nodes, and the restricted endemicity in the rainforest of Central Africa.

Clinical types

There are two main forms of smallpox: variola major and variola minor. The latter has fewer symptoms, a sparse rash, and a case fatality rate of less than 1%. Variola major has a mortality rate of 30%. Two more rare but severe forms are the hemorrhagic and the flat type smallpox. They are almost invariably fatal. The haemorrhagic form is common in pregnant women who develop haemorrhagic rash in skin and mucous membranes. The flat type smallpox results in severe toxaemia and flat confluent skin lesions which do not progress to pustules.

Laboratory diagnosis

Variola is a biohazard group 4 pathogen and all investigations involving its culture and propagation should be done in designated laboratories. The specimens should be collected and handled by

staff who have been vaccinated in the immediate past 3 to 5 years. Suitable specimens include vesicular fluid, skin scabs and blood. Virus can be detected by electron microscopy, culture on chorioallantoic membrane of chick embryo, cell culture and PCR technique.

Management and infection control

There is no specific antiviral treatment available. Investigational drug such as cidofovir has in vitro and in vivo activities but is associated with renal toxicity. The therapy consists of supportive care and antibiotic for secondary bacterial infections.

Patients are infectious from the onset of rash and should be isolated until all scabs are separated. They should be cared for under respiratory and contact isolation in addition to standard precautions. All patient linen and wastes should be decontaminated or incinerated. Surfaces can be decontaminated with freshly-prepared 0.1% sodium hypochlorite.

All close contacts (household or face to face contact), health care workers, laundry, mortuary and laboratory staff handling the patients, their wastes or linen should receive vaccine as soon as possible and preferably within 4 days of exposure. They should be monitored for fever and rash until 17 days after contact.

Vaccination

The smallpox vaccine consists of live unattenuated vaccinia virus (from which the term "vaccination" was derived) which confers immunity through cross reactivity. The efficacy of the vaccine is well proven by the eradication of smallpox. Vaccination is deemed successful if the vaccinee develops at the site of inoculation a progressive reaction which consists of papule, vesicle, pustule, scab and eventually a scar (vaccination "Take"). The duration of vaccine-induced immunity is not certain and most estimates suggest it lasts 3 to 5 years. The vaccine carries a risk of one death per million doses of primary immunisation and causes

serious adverse events such as inadvertent inoculation to other body sites, generalised vaccinia, eczema vaccinatum in vaccinees or their nonimmune contacts with eczema or other exfoliative skin conditions, progressive vaccinia (vaccinia necrosum) in immunocompromised patients and postvaccinial encephalitis. Balancing the risk, WHO maintains its recommendation against pre-exposure immunisation of the general population. Smallpox vaccination is contraindicated in the following groups:

- Persons with history of anaphylaxis to any component of the vaccine
- Persons or household contacts with history of moderate to severe eczema or other exfoliative skin conditions
- Immunocompromised persons
- Pregnant women

In case of exposure to confirmed smallpox, there is no absolute contraindication to vaccination. Vaccinia immune globulin, which is in scanty supply, may be given concurrently (at a different injection site) to prevent development of adverse events in high risk individuals. Vaccination within 4 days of exposure can either prevent infection or ameliorate the clinical illness in the contacts. The world is now better prepared for any bioterror attacks. Contingency plans for control of outbreak has been prepared by WHO, CDC and other authorities. Healthcare workers are educated on how to recognise and better manage smallpox. The vaccine stockpiles are being built up in the next few years. The destruction of variola stock cultures has once again been delayed to facilitate further research on new antiviral drugs and safer alternative vaccines. Any single case will constitute a global emergency. The whole world will be mobilised to prevent the resurrection of this monster.

WHO monograph "smallpox and its eradication": http://www.who.int/omc/diseases/smallpox/smallpoxeradication.html

Viral haemorrhagic fever

M. K. So
Department of Medicine and Geriatric, Princess Margaret Hospital

Background

Viral haemorrhagic fever (VHF) is a general term describing several groups of acute viral infection in which haemorrhage is a cardinal feature of the clinical picture. They usually present with sudden onset of fever, headache and malaise, followed by vomiting, diarrhoea, pharyngitis and maculopapular rash. Development of the bleeding tendency is often accompanied by renal failure, hepatic damage, neurological involvement, shock and multiorgan failure. Most of the diseases are zoonosis with affected humans as accidental host, except dengue haemorrhagic fever and yellow fever. Being an imported disease with unfamiliar features, VHF is always challenging in terms of presenting features, diagnostic methods, management requirements, unexpected complications and unexpected infectiousness in disease transmission. VHF may cause serious consequence in patients. Most VHF causative agents are not transmitted from person to person, though some have caused significant nosocomial transmission and are potential causes of biological disaster. They are Lassa fever, Marburg haemorrhagic fever, Ebola haemorrhagic fever, Congo-Crimean haemorrhagic fever, in approximate increasing order of infectiousness. Person- to-person transmission occurs by direct contact with infected blood, secretions, organs or semen. The risk during the incubation period is generally low, with highest risk during the late stages of disease when patient is vomiting, having diarrhoea or bleeding. Nosocomial transmission is associated with reuse of non-sterile needles and syringes, and associated with provision of patient care without appropriate barrier precautions. Airborne transmission is not important under natural conditions, though it is a rare possibility in advanced disease like extensive pulmonary involvement.

Diagnosis and management

The diagnosis of VHF depends on epidemiological and clinical suspicion, with subsequent laboratory confirmation. Patients should be suspected of contracting VHF if within 3 weeks before onset of fever, they have either

1. Residence or travel in the specific local area of a country where VHF has recently occurred
2. Direct contact with blood, other body fluids, secretions, or excretions of a person or animal with VHF
3. Worked in a laboratory or animal facility that handles haemorrhagic fever viruses.

As the maximum incubation period of VHF is known to be within 3 weeks, the diagnosis can be excluded if more than 21 days has elapsed between leaving the endemic area and the onset of fever. However, one should not overlook more common haemorrhagic conditions because of anxiety about possible VHF, examples are malignant malaria, meningococcaemia, severe rickettsial infections, gram-negative septicaemia with disseminated intravascular coagulation, haemorrhagic chickenpox.

Seeking advice from an ID specialist / clinical microbiologist is desirable when one is managing patient with suspected VHF. In most cases, the diagnosis may be excluded on telephone enquiry with a specialist simply on epidemiological and clinical basis. Otherwise, cases fall into 2 categories when VHF cannot readily be excluded:

1. Medium-risk: Whose investigation should be handled in a center with ID specialist, with the aim of making an altemative diagnosis and treating the patient appropriately.
2. High-risk: in whom VHF is known, obvious or strongly suspected, or is indicated after investigation as a medium-risk case; such case should be referred to ID center with the requisite biosafety facilities and early referral can much reduce the chance of disease transmission.

Laboratory diagnosis is only performed in specialised centres and requires prior consultation with the clinical microbiologist. It is based on demonstrating IgM or IgG antibodies at appropriate stages of the disease. Virus can be recovered from cell culture of the blood or urine. Viraemia can be detected rapidly using PCR techniques.

Infection control

As most ill patients requiring prehospital evaluation and transport are in the early stage of disease, they would not be expected to have symptoms like vomiting, diarrhoea, haemorrhage that increase the chance of contact with infectious body fluids. Universal precautions by the medical, paramedical and ambulance staff are generally sufficient. If a patient has respiratory symptoms like cough and nasal discharge, surgical mask and goggles should be worn by caregivers to prevent droplet contact.

Blood, urine, faeces or vomitus should always be handled as recommended for hospitalised patients. Hospitalised patients should be placed in a private room with a negative pressure to the surrounding. Intensive care support may be needed. An anteroom for attending staff washing and putting on protective clothing is necessary. The number of attending staff should be kept to the minimum and access of visitors is highly restricted. All health care workers should adhere to barrier precautions against airborne and contact infection, especially when coming within 1 metre of the patient. More rigorous precautions e.g. wearing N95 mask is required in late disease. Visible contamination can be cleaned with 1% Clorox (10,000 ppm hypochlorite / 1 in 5 bleach). The recovered patient should be isolated until "virus-free" which in the case of Ebola virus haemorrhagic fever is probably 21 days from the disease onset. Close contact is a person who, after the time of onset of the patient’s illness, have direct contact with the patient’s body fluids, cared for the patient or handled specimens from the patient, or have direct contact with the body of the patient who was diagnosed of VHF. A contact list has to be prepared and all should be kept under daily surveillance for a period of 21 days

from the last date of exposure to infection. Casual and social contacts with the patient before the onset of illness are not at risk in general. Social contact with the patient after the onset of illness should be regarded as 'close contact' and surveillance of the health and temperature during the possible incubation period is sufficient in most cases.

Neurocysticercosis

T. Y. Tsang
Department of Medicine and Geriatrics, Princess Margaret Hospital

Introduction

Neurocysticercosis is caused by brain infection with small bladder like larvae of the pork cestode Taenia solium (T. solium). It is the most frequent helminthic infection of the central nervous system. The word cysticercosis comes from Greek words Kystis (bladder) and Kerkos (tail). Human is the definitive host for adult tapeworm and swine is the intermediate host. Human can also be infected with cysticerci by ingesting eggs excreted in faeces of another infected human. Autoinfection is theoretically possible by reverse peristalsis. Infected subjects always harbour multiple cysts in many parts of the body. Infection of subcutaneous tissue, fascia, muscle and other organs are considered benign. Symptoms arise mainly because of local inflammation. Serious disease is rare except for central nervous system (neurocysticercosis) and cardiac involvement.

Epidemiology

Neurocysticercosis is a ubiquitous disease wherever pigs and humans co-exist. It had once been very common in central Europe, with autopsy identified cysticerci infection rates of 2% in Berlin in first half of 19th century, and 3.5% in Mexico City in the 1950's. It is eradicated from most developed countries, but is still prevalent in Mexico, Central America, Philippines and Southeast Asia. The distribution in Africa is patchy. It is rare in Islamic countries as expected since they do not eat pork. A population study in early 1990's involving 1500 villagers in Mexico showed that 0.3% of the population had stool positive for Taenia eggs. Six percent had history of tapeworm infection and 11% was seropositive to T. solium antigen. Neurocysticercosis is a major cause of epilepsy in endemic area, accounting for up to 50% of epileptic patients in Mexico and 29% in Peru. Neurocysticercosis spread to Papua New Guinea in the 1970's, resulting in dramatic increase in incidence of severe burns related to

individuals falling into domestic fires during convulsion. Risk factors for neurocysticercosis include increasing age, frequent consumption of pork, poor household hygiene and un-tethered pigs wandering around in the environment.

The incidence of neurocysticercosis in Hong Kong is unknown. Seven out of 8 epileptic Gurkhas soldiers in Hong Kong in the late 1980's had cerebral cysticercosis (1). The earliest reported case of neurocysticercosis in Hong Kong was in 1988 by Woo E, Yu YL and Huang CY regarding an infected case who developed cerebral infarct during the course of praziquantel treatment (2).

Life cycle

The eggs of T. solium are evacuated with the faeces to the environment from the infected person. They are ingested by pigs that feed on contaminated food or water. In the small intestine, the embryos hatch from the eggs, penetrate the mucosa, gain access to blood vessels, and travel via the circulation to various tissues, where they differentiate into infective larvae, the cysticerci. Ingestion of the raw pork with cysticerci produces the infection with the adult T. solium in humans. This infection is usually asymptomatic and is only diagnosed by finding eggs or proglottids in stools. Human cysticercosis, however, is a fecal-oral infection acquired by ingesting eggs excreted in the feces of a human tapeworm carrier.

Clinical manifestation

Neurocysticercosis can involve any parts of the brain. The incubation period varies from few months to 30 yrs, but most patients develop symptoms within 7 yrs. The cysts typically enlarge slowly, causing minimal symptoms until years or decades after the onset of infection, when the cysts begin to die. There is no sex preference for the disease. Most the infected subjects are 19 to 35 years old. Thirty percent of the neurocysticercosis has no extra-cranial disease.

Symptoms depend on the site and numbers of lesions, type of cysticercus and stage of development & involution of parasites. Intracerebral lesions may present as mass effect, stroke or encephalitis. Seizure occurs in 50%. Intraventricular lesions may

present as hydrocephalus. Subarachnoid or spinal cord lesions may present as chronic meningitis or cord compression respectively. Intraventricular, spinal cord and basilar cysts cause earlier symptoms by obstructing CSF flow or local meningeal irritation. Psychiatric symptoms can occur in 66%.

Racemose cysticercosis represents an aggressive form of neurocysticercosis. The cysts usually proliferate at the base of brain and appear as a cluster of interconnected grape-like cysts with no scolex. They frequently cause hydrocephalus, local inflammation and mass effects, resulting in mental deterioration, coma and death. Medical treatment is always inadequate and open excision is a better option.

Mechanism of injury

It is postulated that when the cyst dies, they lose osmoregulation and water flushes in. The cyst swells and exerts mass effects over the surrounding brain tissue. Moreover, the dying cysts will also leak antigenic material which can induce severe inflammatory response, causing cerebritis and meningitis. With time the inflamed tissue is replaced by fibrous tissue with complete resorption of parasites. They will then calcify and act as foci of Jacksonian seizures.

Diagnosis

Patients presenting with headache or seizures and have history of travel to endemic regions or history of tapeworm infection should be screened for neurocysticercosis. The presence of subcutaneous nodules in a patient with the above risk factors should also alert to the diagnosis.

Definitive histological diagnosis is not always possible because the parasites are lodged in cerebral tissue. Biopsy of the subcutaneous nodules, if present, may be helpful. Peripheral blood eosinophilia is only identified in 15% of infected cases. Cerebrospinal fluid (CSF) examination may have non-specific elevation of total protein, white cell count and decrease in glucose. Sometimes it may show cellular atypia resembling lymphoma.

Electroencephalogram (EEG) is abnormal in 62% of infected subjects but the correlation of focal EEG abnormality with location of cyst is only 28%. Therefore, accurate diagnosis relies heavily on serological and radiological tests.

Live cysticerci appear isodense (inert) with no contrast enhancement under computer tomographic scanning (CTS). It is most reliable when multiple cystic lesions with scolex are seen. Sole hydrocephalus is present in 20% of neurocysticercosis. Unfortunately, it may still miss 10% of lesions.

Magnetic resonance imaging (MRI) is more sensitive than CTS. It can also demonstrate different activity stages and location of the cysts. The size of the cyst is usually less than 2cm in diameter. Besides identifying the scolex, it can also allow species differentiation. Intrathecal administration of gadolinium is especially good for demonstration of cisternal racemose cysticercosis under MRI. Peri-lesional oedema surrounding calcified lesions can be found in patients at time of seizure. MRI appearance has been correlated with the disease activity. They are divided into different stages as follows:

Stage 1: peri-lesional oedema + nodular enhancement (tissue invasion phase)
Stage 2: CSF-like signal within a cyst (vesicular phase)
Stage 3: thick capsule with an impure liquid content signal and surrounding oedema (cystic phase)
Stage4: disappearance of cystic fluid content signal (degenerative phase)
Stage 5: calcified lesions (residual phase)

Stage 1 will disappear after treatment while stage 4 indicates end of viability and treatment is useless.

Serodiagnostic tests for cysticercus are generally not sensitive and specific since it contains too many conserved antigens in the cystic fluid and wall which can cross-react with antibodies against other cestodes.

Enzyme-linked immunosorbent assay (ELISA) is now widely used, with whole T. solium cysts (obtained from pigs) or cyst fluid as

antigen. Sensitivity and specificity vary according to the population studied, the performance being less impressive in areas of high endemicity or where other helminthes are prevalent. Sensitivity with present ELISA exceeds 80% even in endemic areas but cross-reactivity with other helminthic infections, particularly hydatidosis and taeniasis, remains a problem. A number of purified and specific antigenic tests have been reported but these have not come into general use. More recently, the enzyme-linked immunoelectrotransfer blot assay (EITB) for antibodies detection, using T. solium metacestode glycoprotein antigens, was developed with 98% sensitivity and 100% specificity. In another study, the sensitivity was higher with multiple cysts (94%) and lower for single cyst or calcified cyst (28%). The detection of antibodies and antigen in the CSF in combination with conventional serology marginally improves overall sensitivity. In endemic areas they can be used to screen epileptics and other neurological patients.

Management

Inactive neurocysticercosis lesions should be treated symptomatically. Excision of the symptomatic lesions is difficult since most of them are deep inside the cerebral tissue and most of the infected subjects bear multiple cysts. Surgery is then mainly reserved for the management of complication like hydrocephalus. Therefore medical treatment remains the major modality of treatment. However, cysticercosis is a host response to dying cysts and the role of antiparasitic drug treatment is controversial. Drug treatment itself may also be associated with potential harmful effects, including exacerbation of obstruction of CSF flow, enhancing eye inflammation in ocular disease, increasing the risk of peri-cystic vasculitis with increase in risk of cerebrovascular accident. Case series do suggest that both praziquantel and albendazole hastened clearance of cysticercal lesions, but almost all have some forms of deficits: lack of knowledge of natural history of the disease, inappropriate case inclusion criteria, problems with outcome measure, based only on CTS evaluation, clinical outcome not clearly defined, inappropriate control group, jmprovement may be attributable to steroid rather than antiparasitic drug. One randomized trial indicated that antiparasitic drug with steroid is not superior to steroid alone for long-term control of seizures or resolution of neurocysticerci. Antiparasitic drug group

also had higher complication rate including headache, seizure, and hydrocephalus. The authors conclude that previous reports of favourable response to antiparasitic drug are not definite and may be just the natural history of the condition (3). A metaanalysis including four sizable randomized trials, focusing on the effect of antiparasitic drug in relation to survival, cyst persistence, subsequent seizures and hydrocephalus, concluded that there is insufficient evidence to assess whether cysticidal therapy in neurocysticercosis is associated with beneficial effects (4).

On the other hand, antiparasitic drug for intra-ventricular cysts may prove efficacious, and because of risk of disease progression, antiparasitic drug is recommended. About 80 to 100% of cysts disappear totally with albendazole (5). The dosage of praziquantel for the treatment of neurocysticereosis is 50 mg / kg daily orally for two weeks and that of albendazole is 15 mg / kg orally for eight days. Albendazole is slightly more effective than praziquantel according to some studies. It is important to note that the plasma level of praziquantel increases with inhibition of cytochrome P450 enzyme and high carbohydrate diet. Its bioavailability is also markedly reduced with antiepileptics and steroid. Therefore the suggested dosage for patients who are on steroid is doubled, 100mg/kg daily for two weeks instead. However, the concomitant administration of albendazole with steroid or with praziquantel will increase the concentration of its active form.

Conclusion

Neurocysticercosis is rare in HK. Convulsion is the most common and important presenting feature. Diagnosis requires careful history taking concerning travel, previous episode of tapeworm infection, subcutaneous nodules and family history of headache, seizure or infection. MRI and serology are helpful for diagnosis. The benefit of antiparasitic treatment is controversial. However, Intraventricular lesions deserve drug treatment.

References

1. Heap BJ. Cerebral cysticercosis as a common cause of epilepsy in Gurkhas in Hong Kong. J R Army Med Corps 1990;136(3):146-9.
2. Woo E, Yu YL, Huang CY Cerebral infarct precipitated by praziquantel in neurocysticercosis - a cautionary note Trop Geogr Med 1988:40:143-6.
3. Carpio A, Santillan F, Leon P, et al. Is the course of neurocysticercosis modified by treatment with antihelminthic agents? Arch Intem Med 1995;155(18):1982-8.
4. Salinas R, Prasad K. Drugs for treating neurocysticercosis (tapeworm infection of the brain). Cochrane Database Syst Rev2000;(2):CD000215.

Proano JV, Madrazo I, Garcia L, et al. Albendazole and praziquantel treatment in neurocysticercosis of the fourth ventricle. J Neurosurg 1997;87(1):29-33.

Vesicular skin eruption in a child with Kawasaki disease

Y. W. Kwan and C. W. Leung
Department of Paediatrics, Princess Margaret Hospital

Case

A 4-year-old boy presented with high swinging fever for 5 days, his mother noticed generalised vesicular skin rash since day 3 of the fever. The child was admitted with a presumptive diagnosis of chickenpox. He had no history of preceding drugs or herbal intake, and no definite contact with children with rash. He enjoyed good past health and had no history of dermatological disease.

On physical examination, he was febrile and generalised pustulovesicular lesions (4-5 mm in diameter) in clusters with indurated erythematous base were noted. The rash was tender but not itchy. Other significant findings included bilateral non-purulent conjunctivitis with peri-limbic sparing, red and cracked lips, swelling of the hands and feet and multiple enlarged cervical lymph nodes. The cardiovascular and respiratory systems and abdomen were unremarkable. Investigations revealed total white cell count of 18.6×10^9L and neutrophilia (83.5%). C-reactive protein was elevated (115 mg/ L). Erythrocyte sedimentation rate was raised to 130 mm/hr. Liver and renal functions were normal. Microbiological evaluation for bacterial and viral infections were all negative including blood culture, nasopharyngeal aspirates for immunofluorescence of common viral antigens, throat and stool cultures and vesicular fluid for varicella zoster and herpes simplex virus immunofluorescence.

Dermatologist was consulted. Skin biopsy showed marked neutrophilic infiltration with leucocytoclastic changes and tissue necrosis in the dermal layer. The epidermis is relatively intact with no significant inflammatory infiltration or damage. Parakeratosis is noted. The pathological features were compatible with Sweet syndrome.

The clinical criteria for diagnosis of Kawasaki disease were fulfilled.

Intravenous immunoglobulin together with aspirin were administered with good therapeutic response resulting in rapid subsidence of fever and resolution of all clinical signs including the vesicular skin rash. The clinical diagnosis of Kawasaki disease was further substantiated by a delayed rise of the platelet count to 600×10^9L, which occurred 2 weeks after the initial presentation. Periungal desquamation of the fingers and toes, which is characteristic of Kawasaki Disease were also noted during subsequent follow up. Initial and subsequent echocardiograms were normal.

Sweet syndrome is a rare dermatological manifestation characterised histologically by an acute febrile neutrophilic dermatosis, which presented as painful erythematous infiltrated nodules and plaques on the body of a patient with high fever. The syndrome has been reported to be associated with rheumatic and systemic inflammatory diseases (e.g. sarcoidosis, ulcerative colitis, Crohn's disease and rheumatoid arthritis) and haematological malignancy (e.g. acute myelogenous leukaemia). Kawasaki disease, or febrile mucocutaneous lymph node syndrome, is basically a systemic vasculitic disorder with prominent inflammatory changes affecting medium sized vessels. This is the first report of the association of Sweet Syndrome with Kawasaki Disease. The initial clinical presentation of our patient mimics chickenpox infection and the diagnosis was based on the characteristic clinicopathological features and the exclusion of other causes of vesicular eruption.