

EDITORIAL

Issue Fourteen, Mar 2003

Welcome to our first InfoLink for 2003. This year privacy continues to be a hot topic and in **Pathology FAQ** two of the most often asked questions are answered. If you have additional questions on privacy or indeed any aspect of pathology please send them to us.

This edition contains an article on **Hereditary Haemochromatosis** by Dr Lisa Koe and Anné Proos. The article explores the complexity of this topic and gives guidelines to assist in screening and diagnosis. A second article by Dr George Kotsiou on **Infectious Mononucleosis syndrome** concentrates on the laboratory diagnosis of infectious mononucleosis. Clinicians wishing to avoid the pitfalls of false positive results will find this article most enlightening.

The details of the new collection room at Lane Cove appear below. This new room provides a welcome alternative for patients, saving them the hassle of a trip to the at times congested Royal North Shore Hospital campus. The new collection room is conveniently located near public transport and has ample off street and on street parking.

Thank you to all our readers who replied to our Education Survey. The winner of the prize draw was Dr Rupert Edwards, congratulations. If you did not reply it is not too late as suggestions for articles or seminars are always welcome. Our next issue will include an update on the changed Anti-D guidelines.

The Editorial Team

Editorial Team

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NEW COLLECTION ROOM OPENS AT LANE COVE

47 Tambourine Bay Road, Lane Cove
Ph: 9427-5455

Hours: Monday to Friday 8.30 am to 5.30pm
Saturday 8.30am to 1.00 pm

Hereditary Haemochromatosis

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Hereditary haemochromatosis (HH) is a genetic disorder affecting regulation of dietary iron absorption leading to iron overload in the liver, pancreas, heart and joints resulting in liver damage, failure and cancer, diabetes, heart disease and arthropathy.¹

The HFE gene for HH was identified on the short arm of chromosome 6 in 1996.² It is the most common autosomal recessive disorder in Caucasians with 10% of this population estimated to be carriers.³ Untreated haemochromatosis may be fatal, however, effective therapy can be achieved by removal of excess iron via regular phlebotomy.⁴ HH can be diagnosed before symptom onset, and therapy begun prior to tissue damage, allowing affected individuals to have a normal life expectancy.

Clinical manifestations

Liver manifestations usually appear first and are present in more than 95% of symptomatic patients. Clinical findings include hepatomegaly, fibrosis and abnormal liver function tests.

Diabetes mellitus occurs in about 65% of HH patients, due to excess iron deposits causing direct damage to the pancreas. It is more likely to develop if there is a concurrent family history of diabetes mellitus.

Cardiac manifestations present first in 15% of patients and include cardiac arrhythmias, cardiomyopathy with a diffusely enlarged heart, or overt congestive cardiac failure.

Excessive skin pigmentation is due to melanin and iron deposition, resulting in a characteristic 'bronzed' or slate grey appearance. Pigmentation is usually diffuse and generalised but may be more pronounced on the face, neck, extensor surfaces of the limbs and in scars.

Arthropathy develops in 25-50% of patients, usually as a progressive polyarthritis. The joints of the hands are usually the first joints involved, followed by wrists, hips, ankles and knees.

Hypothalamic-pituitary impairment due to iron deposition results in decreased production of gonadotrophin and other

Table 1. Possible indications for haemochromatosis investigations

Clinical indication	Iron/haemochromatosis testing recommended
1° relative with clinical haemochromatosis or homozygous/compound heterozygous for HFE mutations	HFE mutation testing
Liver disease -enlarged liver fibrosis, carcinoma -cirrhosis, liver failure	Iron indices studies LFTs
Diabetes Mellitus	Iron indices studies
Cardiac disease -cardiomyopathy -arrhythmias	Iron indices studies
Excessive skin pigmentation -bronzed or slate grey	Iron indices studies
Arthropathies -polyarthritis	Iron indices studies
Hypopituitarism -Hypogonadism (amenorrhoea, loss of libido, testicular atrophy, impotence) -Adrenal insufficiency -Hypothyroidism/Hypoparathyroidism	Iron indices studies
Iron overload related conditions -Thalassaemia, Sideroblastic anaemia -Porphyria cutanea tarda Hereditary aceruloplasminaemia Chronic excessive alcohol consumption	Iron indices studies LFTs
Caucasian ethnicity -Healthy -No previous testing -No known relatives with haemochromatosis	Iron indices screen (Testing of healthy populations is currently not rebatable by Medicare. PaLMS has initiated a project 'Optimal Community Screening for Haemochromatosis' offering iron & UIBC screening by referral from participating medical practitioners.)

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hormones. Hypogonadism may present as loss of libido, impotence, testicular atrophy, sparse body hair or amenorrhoea. Other hormone deficiencies include adrenal insufficiency, hypothyroidism and hypoparathyroidism.

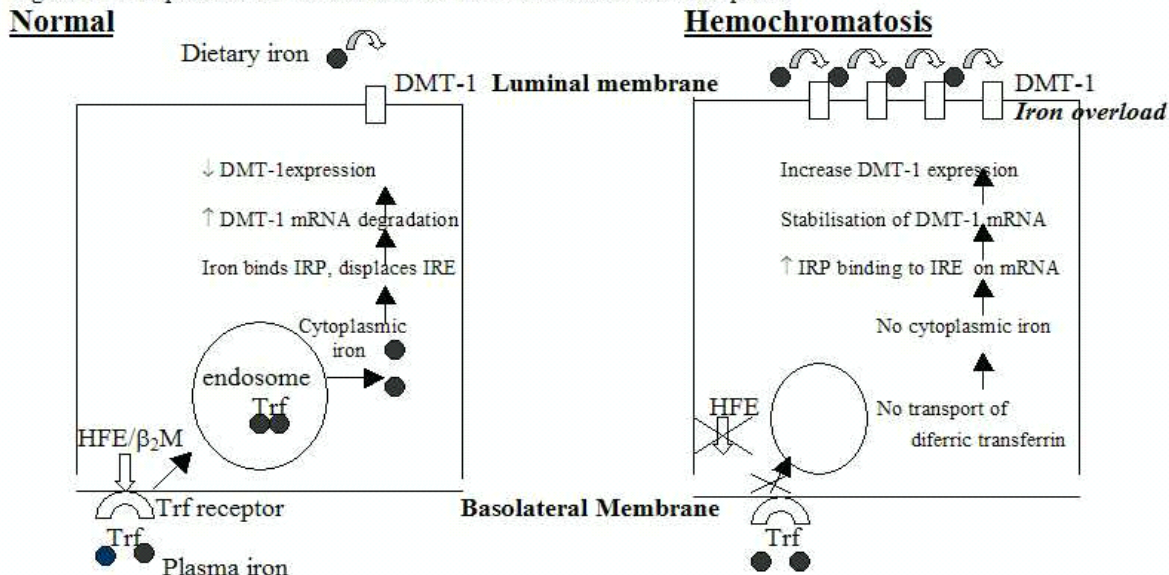
The role of HFE protein in iron metabolism

The normal body iron content is 3-4 g and is maintained by regulation of intestinal mucosal iron absorption to equal iron loss.¹ This loss is approximately 1 mg/d in men and 1.5 mg/d in menstruating women. In HH, daily absorption may be greater than 4 mg. Iron accumulation initially causes plasma iron elevation, increased saturation of transferrin, an iron-binding protein, then progressive increases in plasma ferritin as tissue stores accumulate.

Body iron stores are sensed by the deep crypt cells of the small intestinal mucosa. Within these cells, the normal HFE protein associates with beta 2 microglobulin (β_2M) which facilitates its transport to the cell basolateral membrane (Figure 1).⁵ At this surface, the HFE- β_2M complex associates with the receptor for transferrin and its bound iron, transporting the iron complex into the cytoplasm.⁶ Cytoplasmic iron binds to iron regulating proteins (IRPs) which normally associate with the iron responsive element (IRE) on the mRNA of the divalent metal transporter 1 (DMT-1), protecting the mRNA from degradation.⁷ Dissociation of the IRP increases DMT-1 mRNA degradation, hence decreasing DMT-1 protein synthesis. DMT-1 is the key molecule for iron transport from the intestinal lumen into the mucosal cell.

The HFE gene and its mutations

Figure 1. Comparison of Normal and Hemochromatosis Iron Absorption.



The HFE gene is located on chromosome 6p21.3 and is homologous to the major histocompatibility complex (MHC) class I molecules which are membrane proteins with three extracellular loops, a transmembrane region and a cytoplasmic tail.

Two mutations in the HFE gene were originally identified in HH patients. C282Y disrupts a disulfide bridge in the protein product, which is required for β_2M binding (Figure 2). The result of this mutation is that the HFE protein remains in the Golgi apparatus and is not transported to the surface.¹ Hence, a person homozygous for the C282Y mutation would

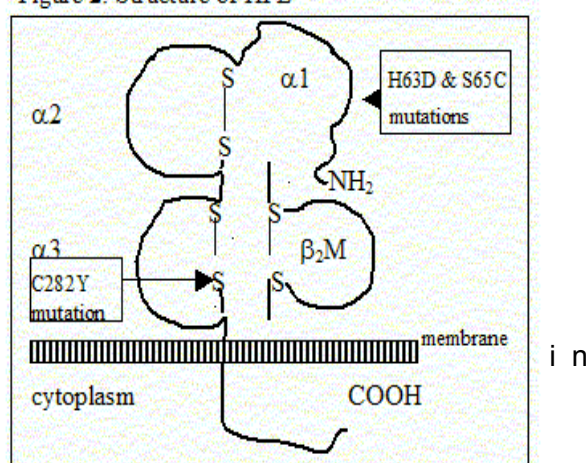
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have no HFE feedback inhibition of iron absorption.

H63D alters the $\alpha 1$ domain, decreasing the affinity of the HFE- β_2 M complex for the transferrin receptor. Hence, there is a milder clinical picture because HFE feedback regulation still occurs, but at a decreased rate.¹ S65C was more recently identified and predicted to have a similar effect as H63D due to their close positional proximity DNA sequence.⁸ The clinical presentation of patients with this mutation has been consistent with this expected milder condition.

Figure 2. Structure of HFE



Currently, there have been 18 mutations (Table 1) and 17 polymorphisms reported in the HFE gene. The majority are rare and several have only been identified in single families. The clinical effect of each mutation depends on whether a viable HFE protein is produced

Table 2. HFE mutations

Designation	Mutation	Reference
C282Y	G845A	Feder et al ²
H63D	C187G	Feder et al ²
S65C	A193T	Mura et al ⁸
V53M	G157A	de Villiers et al ¹⁰
Q127H	A381C	de Villiers et al ¹⁰
E168Q	G502T	Oberkanins et al ¹¹
E168Stop	G502A	Piperno et al ¹²
E169Stop	G506A	Piperno et al ¹²
I105T	T314C	Barton et al ¹³
G93R	G277C	Barton et al ¹³
V272L	G815T	Worwood et al ¹⁴
IVS3+IG→T	IVS3+IG→T	Wallace et al ¹⁵
-7T→C	-7T→C	Douabin et al ¹⁶
R330M	G1198T	de Villiers et al ¹⁰
E277K	G829A	Bradbury et al ¹⁷
V59M	G175A	de Villiers et al ¹⁰
V68ΔT	?del?	Liechti-Gallati et al ¹⁸
P160ΔC	?del?	Pointon et al ¹⁹

and the extent to which β_2 M binding and transferrin receptor interactions are affected. Juvenile haemochromatosis has been recently identified as a separate, rare condition with localisation of the responsible gene to chromosome 1q.⁹ The pathophysiologic mechanisms of this disorder have not yet been elucidated.

Other factors determining iron status

Iron overload may result from other conditions including ineffective erythropoiesis, such as thalassaemia and sideroblastic anaemia, where increased iron demands for haemoglobin production are not met sufficiently rapidly by recycled iron and therefore gastrointestinal uptake is increased.¹ Porphyria cutanea tarda (PCT) is also associated with an increased likelihood of mild increases in parenchymal iron deposits. Alcohol-related chronic liver disease may increase hepatic iron deposition due to cell death and uptake of released iron.

Concomitant HH homozygosity with any of the above disorders increases the likelihood of clinical iron overload. Gross liver deposits are common in HH patients with superimposed alcoholic liver disease. Heterozygote carriers with concomitant conditions are also suggested to have an increased risk of developing clinical symptoms. Heavy alcohol consumption by carriers has been reported to increase risk of hepatic iron overload. Chronic excessive iron ingestion is unlikely to result in iron overload in individuals without a genetic susceptibility, with the exception of a South African black population that consumes a fermented alcoholic beverage brewed in iron vessels.⁴ However, iron

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ingestion is likely to be a determining factor in the clinical penetrance of homozygous or compound heterozygous HH genotypes.²⁰

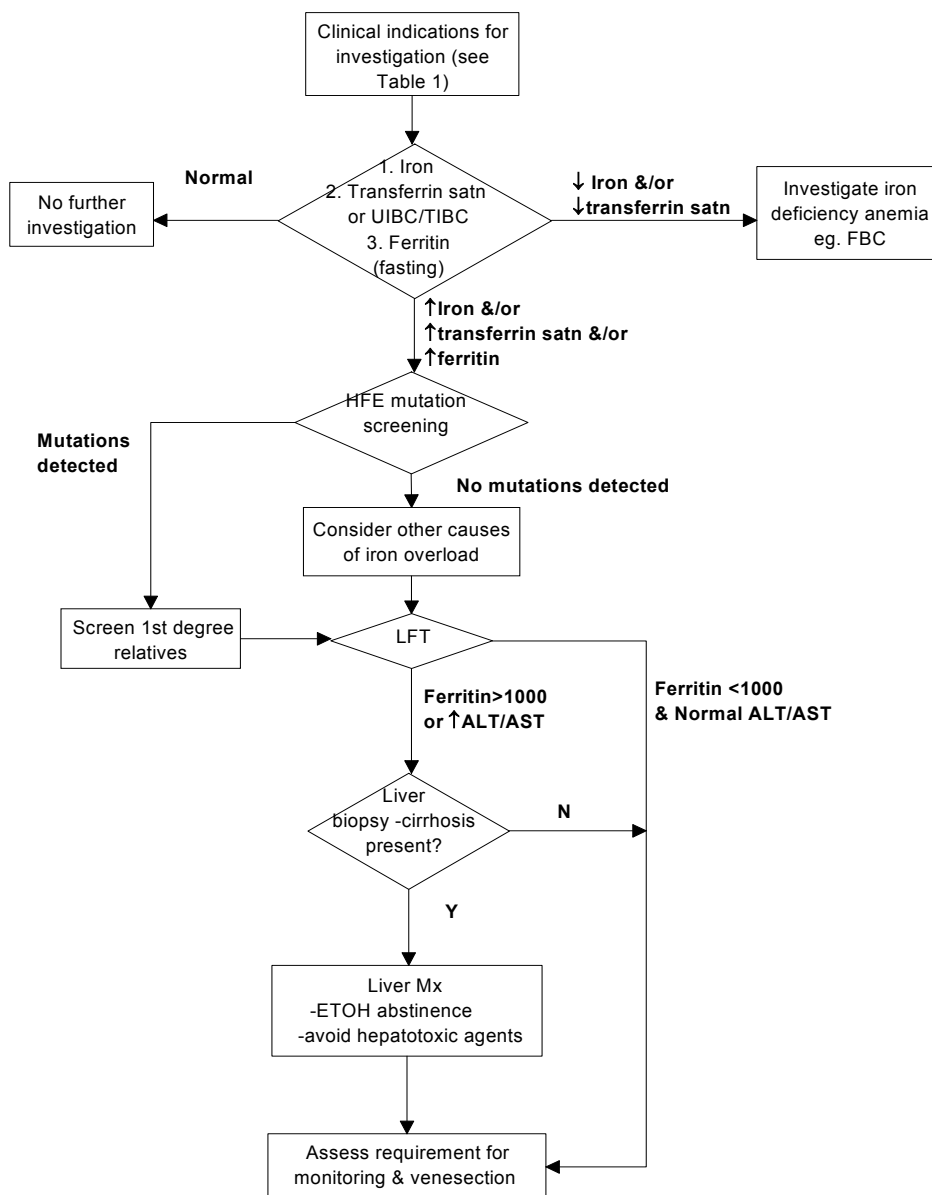
The high male to female ratio of clinical haemochromatosis is attributed to the protective effect of menstrual bleeding.^{4,21} HH homozygote females tend to have a later, post-menopause, onset of clinical disease, with the exception of an early hysterectomy.

Appropriate investigations for haemochromatosis screening and diagnosis

It has been suggested that since HH is a potentially fatal condition and that early detection and appropriate management result in a normal life expectancy, quality of life and work capacity, general population screening would be worthwhile.²²

The clinical penetrance of HFE genotypes, frequency of HFE-unrelated iron overload and cost of phenotyping and genotyping tests, however, all affect the utility and cost-effectiveness of various strategies of screening. Clinical penetrance has been variably

Figure 3. Recommended testing strategy



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reported between 10% and 75%, depending on the population studied, gender ratio, age, diet and geography.^{20,21,23,24} If a significant percentage of such individuals are likely to remain asymptomatic throughout life, the benefits of general population screening may be reduced, as these individuals may be exposed to unnecessary procedures, emotional anxiety, and possible discrimination on a genetic basis. Screening by iron indices studies, for early signs of iron overload, may be more appropriate. Several models for selective screening of targeted populations or case finding in clinical patients who present with related conditions have been proposed.^{23,25,26}

PaLMS provides services for the measurement of iron, transferrin saturation, unbound iron binding capacity (UIBC), ferritin and routine HFE mutation testing for C282Y, H63D and S65C, as well as screening for rare mutations by denaturing high performance liquid chromatography. We currently recommend investigation of patients with clinical presentations which may be related to iron overload (Table 2), targeted investigation of high risk groups including relatives of HH affected individuals and selective screening of the Caucasian population.

Iron indices studies are recommended as the first line tests since molecular testing will not detect HFE-unrelated iron overload conditions. A biochemical index suggestive of increased iron may be followed up by molecular testing as well as a liver function test to determine if liver damage present. Liver biopsy to assess damage and cirrhosis may be indicated if ALT and AST are elevated or ferritin > 1000 µg/L (Figure 3).

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Infectious mononucleosis syndrome

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Introduction

The infectious mononucleosis (IM) syndrome is defined by the clinical triad of *fever, lymphadenopathy & sore throat*. It is commonly caused by the primary infection of Epstein-Barr virus (EBV), one of the family of human herpesviruses. The presence of a characteristic blood picture, a lymphocytosis with large numbers of atypical lymphocytes, may be included as part of the syndrome. Not all elements of the syndrome need occur at any one time in any one patient.

IM remains a common diagnostic consideration following a variety of clinical presentations, particularly in children, adolescents and young adults. This paper will concentrate on issues surrounding the laboratory diagnosis of IM.

Epidemiology

The majority of the world's population have been infected with EBV by adulthood. Surveys have demonstrated that over 90% of adults in USA are seropositive, indicating past infection. Since the property of viral latency is common to all herpesviruses, individuals remain carriers for life and intermittently shed virus in their saliva. At any one time it has been estimated that 15-20% of individuals are excreting EBV. This high background rate of shedding makes isolation of IM cases of little value. The virus is not highly infectious and intimate contact is required for spread. Epidemics of EBV infection are very rare if they occur at all.

EBV infection of an infant is usually asymptomatic. Thereafter the risk of symptomatic disease increases with increasing age. The median age of EBV infection is much later in Western countries, including Australia. This results in a much higher rate symptomatic disease, compared to that observed in developing countries. A post-pubertal peak in incidence is well documented and is presumably related to increased exposure to saliva with the onset of sexual activity.

Episodic cases of infection continue to occur throughout adulthood and also result in symptomatic disease. These cases may be severe and are more often atypical (rather than the classical IM syndrome), particularly in the elderly. Overall IM is much less frequent in adults because of the small pool of susceptible individuals.

There are a number of neoplastic conditions associated with EBV infection. These diseases involve the two main cell lines infected by EBV, B-lymphocytes and nasopharyngeal epithelial cells. They include a variety of lymphoproliferative syndromes (Burkitt's lymphoma, CNS lymphoma in AIDS, oral hairy leukoplakia in HIV and others) as well as nasopharyngeal carcinoma.

Differential Diagnosis

The clinical presentation of IM suggests the diagnosis in the majority of patients. Although there is no specific therapy it is still important to verify this diagnosis. This

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allows one to avoid unnecessary and possibly harmful antibiotic therapy; the well known rash from amoxicillin therapy being a case in point. The diagnosis also provides some prognostic information, which is of great assistance to the patient. Finally, confirmation also serves to exclude other possible diagnoses thereby eliminating the need for costly, potentially harmful investigations and reassuring a worried patient.

Causes of IM syndrome

Epstein-Barr virus
 cytomegalovirus
 HHV-6
 HIV

Toxoplasma gondii
 rubella

 hepatitis A
Streptococcus pyogenes
 drug reaction

While a good history and clinical examination will allow the clinician to make the clinical diagnosis of IM, laboratory investigation is necessary to confirm the aetiology. This is because there are many other conditions, predominantly infectious, that can cause the IM syndrome. It is not possible to accurately distinguish between the various causes on clinical grounds alone, though some features may suggest a specific aetiology. Table 1 lists some common illnesses that can cause the IM syndrome.

Laboratory Diagnosis

Serology is the common method used to make the diagnosis of IM secondary to acute infection with EBV (EBV-IM). There are two types of test available, those that detect non-specific heterophile antibodies and those that measure specific antibodies against EBV.

Heterophile antibodies are produced as part of the hypergammaglobulinaemia that characterises IM. They represent a small proportion of the polyclonal, predominantly IgM response produced by the infected B-lymphocytes. The name 'heterophile' is derived from the fact that these antibodies agglutinate non-human erythrocytes.

A variety of rapid, latex agglutination slide tests are now available for detecting heterophile antibodies (Monospot). These have supplanted the older, gold standard Paul-Bunnell-Davidsohn test, that required multiple absorption steps to improve specificity. The modern rapid tests use purified antigen with high specificity. Their major advantage is that they can be performed quickly on the bench top, allowing a result to be provided while the patient is waiting. However, the interpretation of these tests is subjective and false positives from incorrect reading can be a problem with inexperienced operators.

Heterophile antibodies suffer from a number of disadvantages as a diagnostic test. Not all patients with EBV-IM will have heterophile antibodies at presentation. The antibodies may take some weeks to develop, necessitating weekly testing to maximise sensitivity. Children may not develop heterophile antibodies at all and the same may be true in the elderly or for atypical cases. Alternatively the antibodies may persist for 12 months or more. Overall sensitivity of heterophile tests will vary with the particular test kit, the age spectrum of the patient population and their duration of illness at presentation. Quoted figures for sensitivity vary from 65-85%.

The alternative diagnostic approach is to measure antibodies to specific EBV antigens.

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The most commonly used assay is to measure IgM antibodies to the viral capsid antigen (VCA). Historically an immunofluorescence methodology was necessary, but laboratories now use an enzyme immunoassay (EIA). This allows test performance to be automated, providing an objective result. Testing is normally done in batches at a central location.

Essentially all patients with symptoms due to EBV-IM are positive for VCA IgM antibody at the time of presentation. The sensitivity of the test approaches 100%, a negative result ruling out acute EBV infection in this setting. The rate of false positive results is low but they do occur. They are thought to be due to reactivation of EBV or cross-reactions from infection with other herpesviruses. Further testing for antibodies to other EBV antigens (EBV nuclear antigen, EBNA) will determine whether a questionable result is truly a primary EBV infection.

If a patient with IM syndrome is negative for EBV IgM then it is appropriate to proceed on to further testing. By far the commonest cause of non-EBV IM is cytomegalovirus (CMV), and serology for CMV IgM & IgG should be requested. In some cases CMV culture may also be worthwhile. The diagnoses of toxoplasmosis, rubella and HIV have implications for management and I would normally recommend screening for these agents as well, if clinically relevant. How extensive further investigations should be will depend on other factors such as the severity of disease, patient anxiety regarding the diagnosis and possible implications for contacts. Discussion with a microbiologist or infectious diseases physician may be helpful in determining appropriate further investigation in specific cases.

Summary

A patient presenting with the IM syndrome is most likely to have primary EBV infection and it is appropriate for this to be serologically confirmed. The most sensitive test for this purpose is EBV VCA IgM. Heterophile tests such as the Monospot suffer from problems with both sensitivity and objectivity and, if negative, necessitate a follow-up EBV VCA IgM in any case. In my opinion the specific EBV IgM assay has sufficient advantages over the heterophile tests to recommend it as the first line investigation for IM, despite the slight time delay in obtaining a result. If the test is positive and the clinical context is suggestive of IM then no further testing is warranted.

If negative then testing for CMV IgG & IgM should be requested. This will usually be able to be performed by PaLMS on the original specimen. Depending on the clinical setting other serology may also be appropriate. Most of these tests will require a convalescent specimen in 2-3 weeks for optimal diagnosis, though the initial results may be very suggestive.

Testing of EBV VCA IgM at PaLMS is currently performed on a daily basis on weekdays. The assay is performed by default if the laboratory receives a request for diagnosis of IM. Results will normally be available by the following afternoon, weekends excepted.

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Pathology F A Q

At PaLMS we will at all times strive to protect your patients privacy whilst at the same time ensuring patient care and safety is not compromised. The following questions have been raised by a number of medical practitioners.

- Q: My patient attended a NSH hospital Emergency Department. Pathology tests were ordered and my patient is anxious to know the results. How do I access these results?*
- A: Contact PaLMS on 992 66066 and identify yourself (using your PaLMS Doctor Code). Give your patient's name and date of birth and advise the PaLMS staff member that you are the patient's treating doctor. The results will then be released to you and an entry made on audit trail of the relevant patient episode.
- Q. I have a new patient who over the past two or three years has had various pathology tests via PaLMS. I would like to have those results in my files. How do I organise copies of these results?*
- A. Again contact PaLMS on 9926 6066 and you will be faxed a patient consent form. Once the signed form is returned, the relevant results will be faxed or sent to you according to your preferred method of receiving the reports. This will be recorded in the audit trail of the relevant patient episodes.
- Q. Why the difference in the two scenarios above?*
- A. It is a privacy issue. In the first scenario the results are current and you are involved in the immediate care of the patient. With the second you were not the patient's treating doctor when the tests were performed and the patient has the right to decide what health records are divulged to his/her new treating doctor.

If you have not received your handy wallet size card with your PaLMS Doctor Code please let us know by contacting PaLMS Administration on 9926 8086 and one will be forwarded to you.

To clarify or comment on any privacy issues please contact Margaret Hardy on 9926 8086 or at the email address below.

Send suggestions for FAQs to InfoLink Editor Fax: 9926 6395 or Email: mkhardy@doh.health.nsw.gov.au

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