



IDENTIFYING HAEMOCHROMATOSIS

patients in your practice



Early intervention in haemochromatosis is known to significantly improve life expectancy and quality. For this reason, identification of previously undiagnosed cases is important. The two ways of identifying those who need further testing are clinical selection and investigation of persons with a positive family history. Once identified, the next step is investigation with iron studies and in some cases genetic testing. In some patients assessment and diagnosis by liver biopsy will be appropriate.

The benefits

Early identification and management of these patients will benefit them by avoiding the build up of damaging iron within vital organs. Awareness of the disease and recognition of the variable nature of possible presentations will improve the doctor's ability to select appropriate patients who require further testing.

Selecting who to test:

The role of clinical suspicion and family history.

Clinical Suspicion

Some patients with haemochromatosis will already have developed abnormal iron studies. Iron studies (perhaps performed for another reason) which show unexpected high saturation or raised ferritin may suggest genetic haemochromatosis. Some features of organ damage, for example serum enzyme elevations from liver damage, diabetes mellitus from pancreatic damage, or arthropathy from cartilage damage, raise the suspicion of underlying genetic haemochromatosis as a possible cause.

Family History

To identify the condition before it is clinically evident the family history is an important feature to pursue. If a

Haemochromatosis Clinical Features OVERVIEW

Organ Affected	Possible Manifestations
Liver	Raised liver enzymes, cirrhosis
Pancreas	Diabetes mellitus
Cartilage	Joint pain, chondrocalcinosis
Pituitary	Pituitary failure, 2° hypogonadism, loss of libido
Skin	Bronze pigmentation
Heart	Cardiomegaly, heart failure, arrhythmias, conduction defect

Other possible features are an unusual degree of fatigability, abdominal pain, or hepatocellular carcinoma occurring in longstanding haemochromatosis.

sibling is affected then it may be expected, that on average, one in four of the other sibs will have the condition. If the family relationship is more distant than first degree then the likelihood of Genetic Haemochromatosis is closer to the background population risk (the average population risk of Anglo-Celtic Australians being affected by Genetic Haemochromatosis is 1 in 200).

How to test (what to request)

DNA testing

DNA testing for the mutations causing Genetic Haemochromatosis is indicated (and Medicare rebatable) if the patient:

- has an elevated ferritin or transferrin saturation on testing of repeated specimens
- has already been diagnosed by some other means as having Genetic Haemochromatosis
- has a first degree relative who has clinical Genetic Haemochromatosis or who has been shown by genetic testing to have two copies of recognised mutations. In this situation, having recently performed iron studies is often helpful in assessing the implications of the genetic results.

DNA testing at QML reports the mutations C282Y, H63D, and S65C – for details on mutations see the mutation overview.

Iron studies

Iron studies without DNA testing should be the initial test when Genetic Haemochromatosis is suspected in situations other than those listed above. The ideal collection for iron studies is a fasting morning specimen because diurnal variations and oral intake can affect the pattern of iron results. However, non-fasting results are often adequate for assessment.

Interpreting results

All DNA results and abnormally raised iron studies will have interpretive comments added using the context of the provided clinical notes. Here are some common patterns of results and their brief interpretation:

Iron Studies abnormally raised

An elevated ferritin or transferrin saturation on testing of repeated specimens (ie. two or more) is an indication for proceeding to genetic testing unless the results can be confidently ascribed to another cause alone.

Because DNA testing requires the white cell fraction of the blood specimen, DNA testing should not be performed on specimens previously opened for other tests. A further collection of a DNA test sample (EDTA whole blood) therefore, is usually required.

Two haemochromatosis mutations

As Genetic Haemochromatosis is an autosomal recessive condition, two mutations (one on each Chromosome 6) indicate that the genetic makeup for the disease is present. Whether this results in clinical disease depends on the particular mutations found and the patient's iron balance.

Patients with two C282Y mutations (homozygous for C282Y) are more likely to develop the disease than someone with one C282Y and one H63D or with one C282Y and one S65C (because H63D or S65C act as "milder" mutations).

Due to natural physiological iron loss, females may have some protection from iron overload due to menstruation and pregnancy and they may not accumulate iron until after the menopause.

One haemochromatosis mutation

This almost always indicates that the patient is only a carrier of haemochromatosis and will not have Genetic Haemochromatosis. The exception to this is when a rare undetectable mutation is also present. If this situation is suspected because of abnormal iron studies or a family history of an uncharacterised mutation, then further investigations can be discussed with a Pathologist.

Implications for other family members

When genetic information becomes available for a patient, it has implications for other family members. Advising the patient of this fact and encouraging them to communicate with others who may benefit from the information is important. The patient's siblings are the ones to whom the information will be most directly useful, because siblings of an affected patient have at least a one in four chance of having the same genetic make up.

DNA testing is indicated in general only once in a patient's lifetime, but if there is any concern regarding apparently discrepant results within a family or if a new mutation has been

Mutations in the HFE gene OVERVIEW

The accepted name for the gene causing Genetic Haemochromatosis is "HFE". The tested mutations are:

- **C282Y** This mutation is present in 90% of clinical cases, with two copies commonly leading to clinical expression if not treated.
- **H63D and S65C** These act as mild mutations that can produce iron overload if occurring with a C282Y or less commonly if they occur as two mild mutations together. The S65C mutation was only recently discovered and its status is still being evaluated but it currently is believed to be even milder than the H63D in effect.

Some rare Haemochromatosis mutations have been described for which genetic diagnostic testing is not clinically available. Contact the Pathologist to discuss testing if such a situation is suspected.

What does the name C282Y mean?

"C282Y" means that the coding for the amino acid **C**ysteine that is usually coded at position **282** in the gene is replaced with coding for **T**yrosine instead.

added to the laboratory's repertoire, retesting may be indicated. I mention apparently discrepant results because genetic testing has the possibility of revealing paternity discrepancies. As well as paternity being unclear, occasionally true maternity may have been concealed for family reasons.

Most apparent genetic discrepancies within a pedigree turn out to arise from communication of incomplete or misunderstood information between family members (eg. a carrier may be said to 'have' haemochromatosis by a lay person) - so careful review of the family genetic details is necessary. Referral for formal genetic review and counselling may be indicated in some cases.

Current role of liver biopsy

Liver biopsy should be considered in individuals homozygous or compound heterozygous for the C282Y mutation that meet at least one of the following criteria:

- Serum ferritin greater than 1000
- Abnormal serum aminotransferase levels (ALT, AST)
- Hepatomegaly
- Aged over 45 years

Treatment Initiation

Suggested serum ferritin levels at which therapeutic phlebotomy should be considered in individuals with hereditary haemochromatosis (from Vautier et al. 2001):

Age under 18 years (both sexes)	200 ug/L or greater
Woman 18 years or over (menstruating)	200 ug/L or greater
Postmenopausal woman	300 ug/L or greater
Man 18 years or over	300 ug/L or greater

References

Vautier G, Murray M, Olynyk JK. Hereditary haemochromatosis: detection and management. Med J Aust 2001; 175:418-21.

Barton JC, McDonnell SM, Adams PC, et al. Management of hemochromatosis. Hemochromatosis Management Working Group. Ann Intern Med 1998; 129:932-9.

Asberg A, Thorstensen K, Hveem K, et al. Hereditary hemochromatosis: the clinical significance of the S65C mutation. Genet Test 2002; 6:59-62.



Dr Nigel Brown DipRACOG FRCPA

Dr Brown joined QML Pathology in May 1999 as Consultant Chemical Pathologist in the Biochemistry Department of the West End laboratory.

A graduate of the University of Queensland (1980), Dr Brown trained in pathology at the Royal Brisbane Hospital before obtaining his fellowship in chemical pathology in 1989.

He remained at the Royal Brisbane Hospital for nearly a decade where, in addition to general chemical pathology, he explored his interests in genetics and errors of metabolism.

Special Interests: Liver Biochemistry, Inborn Errors of Metabolism, Computational Biology and Drug Response Genetics.



SARS

Severe
Acute
Respiratory
Syndrome

by Dr David Drummond

Severe Acute Respiratory Syndrome (SARS), at this present moment in time, appears to be caused by a virus. The most likely candidate being a newly discovered member of the Coronavirus family. This new agent does not fit into any of the known sub groupings of the family. Other members of this family are common and in humans are principally associated with "colds". Occasionally they have been found in association with diarrhoea and lower respiratory tract infection. The family is not restricted to human hosts. Other animals such as rodents, domestic fowl and pigs can be infected by other sub groups of the family. To date there has not been any evidence of cross species transmission of Coronaviruses. Whilst this new virus is the prime suspect, it should be borne in mind that in some of the suspected SARS cases other viruses such as Human Metapneumovirus has been found in lung tissue of suspected cases.

With the progress of time some of the epidemiology of the epidemic is becoming clearer. The first cases seem to have appeared in China late last year. At the end of February 2003, the first cases appeared in Hong Kong following the stay of an infected traveller. Since that importation two events occurred.

The first was an explosive outbreak in the Kowloon Bay area of Hong Kong. This occurred in an area of high density housing with poor sanitation and infested with vermin. High attack rates were observed and this resulted in the widely publicised strain on the Hong Kong hospital system.

The second event was the concomitant appearance in other countries of patients, infected or suspected. Understandably, there was great concern over the appearance of a new disease associated with a not insignificant mortality rate. The causative agent clearly had the potential for epidemic and possible pandemic spread. The global community acted through the auspices of the World Health Organization and quarantine measures were introduced as well as other measures to limit the transmission and spread of the infection. These measures were applied

locally and globally. At the same time there was intensive international collaboration aimed at understanding not only the epidemiology, but also elucidating the cause and developing a diagnostic test. This remarkable effort resulted in the discovery and elucidation of a significant amount of molecular information of this new virus within a few weeks.

Clinically, the incubation period lies between 3 to 10 days. All patients initially present with a cough and most complain of myalgia and or lethargy. On examination there is minimal auscultatory findings. A chest X-ray initially may show very little other than localised areas of patchy infiltrates. Findings that can be associated with many atypical pneumonias. There may a slight rise in the serum transaminases and a mild leukopenia and lymphopenia. In the cases in the Kowloon area, diarrhoea was a common finding, but this has not been noted elsewhere.

The information to date indicates the following. The lungs are the prime focus of infection but the mild changes in the liver transaminases suggests the possibility of some period of viraemia during the course of the illness. The infection is spread principally via droplets. Faecal - oral transmission might occur, as suggested from the Hong Kong experience and is seen in other members of this virus family, but it is probably not the major route. Prolonged contact with the patient or a contaminated environment appears to be necessary for transmission. It is unknown if there is an animal reservoir for this virus but the possibility is being investigated. China remains the prime focus of the epidemic whilst globally the numbers of cases are falling or slowing and secondary spread appears to have been brought under control.

At present there is no specific antiviral therapy and management is centred on respiratory support and preventing transmission. It is unlikely that a suitable vaccine will be available in the near future. Previous work on developing a vaccine against other Coronaviruses has been disappointing and preliminary work with the SARS virus is indicating substantial difficulties due to the genetic nature of the virus.

The mortality rate is a subject of current debate. The overall mortality rate is of the order of 5 to 10%, however these figures were derived early in the epidemic and are skewed by the explosive outbreak in Hong Kong and the uncontrolled epidemic in China. It is also clear that the elderly and those with other comorbidities have a higher mortality. Lastly the current case definitions are not as stringent as one would like.

From the experience and evidence of those managing cases, it is quite clear that adherence to standard infection control measures with additional respiratory precautions in association with patient isolation and terminal cleaning of infected patient's rooms are crucial in protecting patients and staff.

The virus can be detected by reverse transcriptase polymerase chain reaction (RT-PCR). Suitable specimens are bronchoalveolar lavage, faeces, urine and sputum. It would appear that nasopharyngeal aspirates and throat swabs have lower amount of virus compared to the former specimens. The test may be negative initially and should be repeated if the infection is still thought to be a possibility. This test is available in Queensland. Other tests such as detection of antibody are not available at present.

As more and more information is accumulated national health agencies and the World Health Organization regularly update information for the public and health professionals on their websites.

<http://www.who.int/en/>

<http://www.cdc.gov/ncidod/sars/>

<http://www.health.gov.au/sars.htm>

The Commonwealth Department of Health and Ageing has established a national information phone line for enquires from the public. The phone line will be staffed seven days a week from 9am to 8pm EST. Call 1800 004 599.

**The above information was accurate at 1000 hours 28th April 2003.*



Skin Deep CPD

QML, in conjunction with the Wesley Hospital, held a CPD evening on Thursday, 10th April in the Wesley Auditorium. The CPD was entitled 'Skin Deep', with topics including Dermatoscopic Evaluation of Pigmented Lesions, Bullous Diseases and Melanocytic Lesions.

Approximately 70 doctors attended the evening, enjoying dinner and refreshments provided by the Wesley and QML while receiving 2 points per hour from the RACGP. The speakers on the night were Dr Rohan Mortimore, Dr Karyn Lun and Dr James Muir who were enthusiastically received by the audience of doctors from around Brisbane.

The 'Skin Deep' CPD was the first event in the educational calendar for QML, with many more professional development seminars planned for the year in different regions throughout the QML network.

CYTOLOGY NEWS

New Pap Pricing

As of May 1, 2003, the price of ThinPrep will be increased from \$22 to \$29.

This price rise was due to significant price restructuring by the suppliers of consumables used in testing.

In an effort to maintain affordability for your patients, the cost of PAPNET will remain at \$20. Also, when combining PAPNET with ThinPrep testing, patients will pay only a \$1 extra, receiving both comprehensive screening services for \$30.

Taking effect from 1 May 2003, these new changes are similar to those of other laboratories. If you have any queries please contact QML Liaison on (07) 3840 4539.

Plastic Spatulas

Please note that all PAP Collection Kits which presently contain wooden spatulas will soon be replaced by plastic ones. The new kits will be available as soon as current stocks are depleted, which is estimated to within the next 1-3 months.

If necessary, both wooden and plastic spatulas will be available as single items if required by referring doctors.

If further information is required please contact QML Cytology (07) 3840 4485.

Congratulations to QML Collectors

St Andrew's Hospital at Ipswich has recently completed a survey of patients, with all feedback received helping to enhance the provision of services to their community.

The survey results showed that all QML collectors who visited the Hospital rated extremely well, with the staff being rated in two areas:

- ✓ Skill of the collectors
- ✓ Courtesy of the collectors

In both areas, QML rated above the private hospital benchmark and surpassed the previous survey result by a large margin.

UPCOMING EVENTS

The Australia Association of Practice Managers & QML Pathology are proud to present

STAFF DEVELOPMENT DAY 2003

"Staff DO make the difference"

Saturday, 24 May 2003
Hilton Hotel, Brisbane

For further information, please call the AAPM on (07) 3257 3930

ST ANDREW'S CPD WEEKEND 24-25 May Marriott Hotel, Gold Coast

Topics include:

- Thoracic Spine Workshop
- Excision Techniques
- Leg Pain
- Headaches
- Abdominal Pain

Please contact the St Andrew's Marketing Department on (07) 3834 4210 for further information.

QML Pathology.

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Doctors' Notice Board

Associate Professor Ken Armstrong, has expanded his practice with new rooms at the Sunshine Coast while continuing his current practice at Ashgrove. From June 2003 he will be available at Boulevard Centre, 68 Jessica Boulevard, Minyama. Professor Armstrong offers expertise in the areas of developmental and behavioural paediatrics, sleep disorders, maternal mood disorders/infancy and forensic paediatrics/court reports. For appointments please telephone: Ashgrove (07) 3510 2176 or Sunshine Coast (07) 5452 6611.

Drs Ian and Ann Crawshaw, wish to advise that they have ceased consultant paediatric practice at North West Specialist Centre, Everton Park and are continuing paediatric practice in Canberra. They wish to thank their referring obstetric and general practice colleagues for their support and their subspecialist paediatric colleagues for their assistance.

Dr Robert Liong, a specialist in the treatment of neuromusculoskeletal pain such as headaches, neck pain, shoulder, elbow and arm pain, back pain including "sciatica", hip and knee pain (treatment includes various modalities of physical therapy and pharmacotherapy when indicated), has commenced sessional practice at Caloundra Sports Medicine Centre. For enquiries please telephone (07) 5491 1144.

Dr Mahomed Khatree, Obstetrician & Gynaecologist, is now consulting at both Logan Private & Sunnybank Private Hospitals. For all enquiries, appointments and maternity bookings, please phone (07) 3804 4585 (Logan Private) or (07) 3344 9453 (Sunnybank Private).

Dr David Levitt, Paediatrician, has commenced practice at the North West Specialist Centre, 137A Flockon Street, Everton Park. For appointments please telephone (07) 3353 0467.