Hereditary haemochromatosis: never seen a case?

HEREDITARY haemochromatosis (HHC) is a disorder of excessive absorption of dietary iron leading to deposition of iron and resultant dysfunction in several organ systems. Described originally by von Recklinghausen in 1889, it has traditionally been considered a rare disease characterised by the classic triad of cirrhosis, diabetes, and skin pigmentation, or 'bronze diabetes'. The discovery of the genetic basis for HHC[1] has led to a re-evaluation of the belief that the disease is rare and the possibility that it is being underdiagnosed.

HHC is an autosomal recessive condition and in 90% of cases in the United Kingdom (UK) the condition is owing to homozygosity for the C282Y mutation in the *HFE* gene.[2] A second mutation in the *HFE* gene, H63D, can cause the disease when in the presence of a single C282Y mutation (the so-called 'compound heterozygote' state). These mutations are common in people of Northern European origin with a carrier frequency of the C282Y mutation of one in 10–17, in the UK, suggesting a prevalence of people homozygous for the C282Y mutation of between one in 100 and one in 280.[3] If HHC becomes symptomatic by mid-life, a general practitioner (GP) with a list size of 2000 patients should have approximately four cases. In our experience most GPs claim to have never seen a case. Herein lies the conundrum: is HHC far more common than is currently recorded in clinical records and death registers because it is not being diagnosed, or does significant disease not develop in a large proportion of C282Y homozygotes and compound heterozygotes?

Early symptoms of HHC are frequently non-specific, such as fatigue, arthralgia, and abdominal pain and only later do features such as diabetes, impotence, cardiac failure, arrhythmias, amennorhoea, and skin pigmentation develop. Consequently diagnosis is often delayed. In a United States survey of 2851 patients with HHC, symptoms had been present for an average of 10 years and two-thirds of patients had been given an alternative diagnosis before HHC was diagnosed.[4] The disease is diagnosed initially on the basis of persistently raised transferrin saturation, followed by evaluation of iron overload with serum ferritin measurement and, in some circumstances, liver biopsy. If left untreated the disease has survival rates of 18% and 6% at five and 10 years after diagnosis, respectively.[5] However, if treatment by therapeutic phlebotomy is instigated before the onset of cirrhosis or diabetes, a normal life expectancy is achievable.[6]

HHC appears therefore to be a common disease that is frequently diagnosed late and for which there is a simple diagnostic test and effective treatment. Not surprisingly, there have been calls for population screening for HHC[7] and several studies, including some based in primary care, have evaluated a range of different screening strategies and diagnostic criteria.[8-10] These studies have shown a prevalence of C282Y homozygotes of 34 men and 40 women per 10 000, of whom 50% and 44% had clinical manifestations, respectively. Decision analysis models demonstrate that population screening for HHC is cost-effective across a wide range of assumptions about prevalence and test costs.[11] However, several issues remain before population screening for HHC meets accepted criteria for a screening test.[12]

Perhaps the most fundamental issue is that the natural history of HHC and, more specifically the homozygous state, is poorly understood. Allied to this is the central point of case definition. A key argument in favour of population screening is the relatively high frequency of C282Y homozygotes but it is unclear what proportion of these will develop iron overload or significant life-threatening or life-impairing symptoms. This makes it vital that, when discussing screening, the decision to define a case based on either genetic, biochemical or clinicopathological criteria is made clear.

The choice of which test to use in population screening is uncertain. Should it be a biochemical test (i.e. transferrin saturation), that is currently cheaper and only identifies those with evidence of gene expression, or should it be a genetic test that will identify those before iron accumulation occurs and is more specific (in that transferrin saturation inadvertently screens for iron deficiency)? The use of a genetic test may have greater implications for other family members since it will identify heterozygotes who will require additional counselling. This would include offering the test to siblings and partners and discussion of the possibility that the heterozygous state may be associated with an increased risk of type II diabetes and coronary heart disease.[13,14] A genetic test may also have a greater impact on applications for insurance than a biochemical test would.[15]

Although therapeutic phlebotomy is effective in terms of mortality, it requires frequent visits, usually to hospital and may not alter the patient's symptoms. Fatigue improves in about half of patients but arthralgia and impotence rarely improve and may in fact deteriorate after phlebotomy.[4] As HHC is a multi-system disease, secondary care services are sometimes fragmented, with care organised through a range of disciplines, such as gastroenterology, haematology, or clinical genetics. A well co-ordinated multidisciplinary service covering all these specialties would be necessary to support a population screening programme for HHC. Some of the difficulties faced by a GP and her patient diagnosed with HHC through a screening study are well described in a recent case report that questions the utility of diagnosis and treatment of 'asymptomatic HHC'.[16]

The most important question of disease expression will be answered by cohort studies, currently in progress, of C282Y homozygotes and compound heterozygotes. In the meantime it is generally accepted that population screening for HHC should not be adopted into routine care.[17,18] An interim proposal is that clinicians, and specifically those in primary care, should be more aware of the possibility of HHC as a cause of a wide range of symptoms and diagnoses. Box 1 lists conditions and symptoms proposed at a recent consensus meeting where a biochemical test to exclude HHC should be considered.[17] In the report of this meeting it is

Diagnoses
- Diabetes mellitus types I and II
- Cardiomyopathy and arrhythmias
- Chronic parenchymal liver diseases, including hepatocellular carcinoma
- Anterior pituitary failure
- *Porphyria cutanea tarda*

Symptoms
- Arthritis and arthralgia
- Impotence and loss of libido
- Amenorrhoea
- Inappropriate increased skin pigmentation

Box 1. Conditions where a biochemical test to exclude hereditary haemochromatosis should be considered, according to a recent consensus meeting.[17]

suggested that educational campaigns to raise awareness in primary care might lead to early detection of HHC and avoid the need for population screening. But is it possible, within the ocean of common, poorly defined symptoms that constitutes this condition, for primary care to identify those that might be owing to HHC and those that might have some other equally plausible explanation? Will any single symptom, or even symptom cluster, in primary care have sufficient predictive value for HHC to be of clinical value? Selective testing of people with more certain diagnoses may be more appropriate but early evidence is not encouraging, at least for diabetes or abnormal liver function tests.[19,20]

Primary care is faced again with the dilemma of trying to diagnose a potentially common, serious disease, for which there is effective treatment if started early, on the basis of non-specific symptoms or end-stage diagnoses. At the same time it must attempt to limit healthcare costs by the judicious use of investigations. It is quite possible that most GPs will unknowingly have encountered a patient with symptoms owing to HHC but what proportion of such patients progress to develop serious complications of the disease is unknown. HHC highlights the question: when does a genetic predisposition become a genuine disease? The new genetics presents primary care with new diagnostic challenges. Whether HHC can be detected early enough through an active case-finding approach remains to be seen.

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The case for strengthening education and training for general practice

THE need for more general practitioners (GPs) and GP registrars has been recognised. Recent discussions among the bodies we represent and others have led to a proposal for strengthening education and training for general practice in England and Wales. The proposal includes two key strands, which would:

1. enable the extension of the standard period of the general practice element of GP vocational training from 12 to 18 months; and
2. implement a managed system of higher professional education for all GPs in the first two years of their practice, irrespective of their employment status, i.e. principals and non-principals.

Both programmes would be optional in the first instance, introduced on a pilot basis, and evaluated. These initiatives would complement the proposed new arrangements for continuing professional development, strengthening the education and training for general practice across the board — from trainee to experienced GP. The precise arrangements might need to be modified in the light of the review of the senior house officer (SHO) grade, but the principles would still apply.

Extending the general practice element of vocational training

The present three years' duration of vocational training, with one year spent in general practice, was always a compromise. There is extensive evidence to suggest that the two-year hospital component could be improved;[1] however, the expanding educational needs of new GPs in areas such as population medicine, health informatics, clinical governance, research and development,[2,3] and the increasing complexity and demands of the year in general practice, will not be addressed by the — albeit much needed — improvements in the hospital placements.

An evaluation of a recent Scottish initiative in which 35 GP registrars had an extra six months in general practice, although not providing conclusive evidence on improved outcomes, does provide some pointers for the future.[4] In comparison with controls, the doctors who had extended vocational training appeared to be more successful at addressing self-identified gaps in their knowledge and skills and gained in their confidence in practising general practice. The option was popular with the GP registrars. In a recent survey in Wales,[5] over 70% of trainees stated that they would like the opportunity to extend their training.

Patients' desire for a doctor who listens and takes their problem seriously is a consistent message from survey after survey.[6] Doctors having an extended period of practice-based training would have enhanced communication skills. They might also be more confident tolerating uncertainty, thereby protecting patients from unnecessary investigations, referrals, and medication which would incidentally save money for the NHS overall. Finally, it is possible that offering extended vocational training might encourage doctors to take up posts as principals sooner than they do at present. Currently, only 67.7 % of men and 45.8 % of women doctors take up principal posts within two years of completion of vocational training.[7]

There is substantial variation in the duration of training across the member states of the European Union, ranging from two years' training (the minimum allowed under European Council directive 93/16) in Iceland, Belgium, and Italy, to five years in Norway.[3] However, longer periods of the general practice element of vocational training are found in Europe and elsewhere in the world. In Australia and Holland, the programme is three years in duration with one year spent in hospital-based rotations specifically attuned to general practice. Among the Scandinavian countries, there is a five-year programme in Finland with two years spent in practice; a four-and-a-half-year programme in Sweden with two years spent in practice, and a five-year programme in Norway with four years spent in practice .[8]

The paucity of evidence from the United Kingdom (UK) results from lack of opportunity to test the model. A mechanism that allowed pilot schemes to be rigorously evaluated could help determine whether the theoretical benefits accrue in reality. One option would be to create a limited number of slots that could be filled by giving first preference to doctors on the basis of educational need and thereafter through competitive selection. Restriction to struggling registrars might lead to stigmatisation[4] and skew any evaluation.

Such an initiative need not affect any future decision on whether general practice in the UK should be developed as a specialty under Title 3 of European Council Directive 93/16, or remain under Title 4.[9]

Higher professional education

For a variety of reasons — including the need to develop primary care, the need to develop academic general practice and the perceived need for a period of higher professional education following vocational training — a number of post-vocational schemes have arisen. Thus, experience in this arena in the UK is much greater than with extended vocational training.[10] The schemes fall into two broad categories — those that provide salaried full-time posts incorporating service general practice and higher professional education and those that offer forms of part-time higher professional education for new GPs.

Many new GPs, while confident in the clinical skills and abilities gained during vocational training, are not confident that they can properly manage the requirements imposed by becoming a principal in general practice.[2,11,12] Most ultimately become principals, though some decide never to enter partnership. Many spend time working as assistants or deputies (locums) to ease the problems of transition.[7,10]

The salaried schemes in Durham, Liverpool, London, and Scotland have a number of features in common: salaried posts, fixed term contracts (of one to three years), protected

time for further education, mentoring, collective small group learning, opportunities to learn new clinical skills, exposure to a small number of different practices, and opportunities to learn about non-clinical GP activities in management or research.[13] The doctors doing higher professional education within these schemes have been shown to gain confidence, wider experience than just consulting with patients, management skills, and advanced clinical skills and educational attainments, including higher qualifications. They become more willing to enter practice as principals.[14]

There are reservations about whether a small number of full-time posts is the best way to provide this training.[15] Alternative options include distance learning and part-time courses for more doctors for the same amount of funding, and there is experience in the provision of part-time higher professional education for new GPs;[10] for example, MSc and diploma level courses.

Blurring the edges of the current sharp transition from registrar to practitioner, and extending the training principle into the early years of practice, would enable the new GP to build lifelong learning into practice. The doctors would also be provided with a source of personal support through a GP mentor. Higher professional education is therefore very different in outlook to vocational training and is focused on inducting the doctor as an independent practitioner. Care would need to be taken to avoid higher professional education being interpreted by new GPs as another imposition.

The programme would need to be supported by an allowance to cover locum and educational costs (akin to the existing arrangements for general practitioners' prolonged study leave). It is estimated that higher professional education would involve the equivalent of 30 days in each of the first two years of practice.

Conclusion

As nearly 90% of all the problems brought to the health service are contained in primary care, even a small decrease in general practice's ability to contain these problems would hugely increase costs in the hospital service. We argue that investment through these proposed initiatives in 'the human capital' of general practice is likely to yield important dividends in improved patient care, higher morale and expertise among the primary care workforce, and improved recruitment.

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