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Source(s) of Funding:
None

Competing Interests:
None

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Abstract

Background: 0.05% of those with Northern European lineage carry homozygous mutations in the HFE gene causing iron overload. This is a disease with considerable morbidity, which can be screened for. There are many national and regional protocols in place which are somewhat incongruent with each other. We believe that many of the current guidelines are out of date and piecemeal in places and differing regions and consultants are managing this condition in varying ways.

Method: We formulated a questionnaire for Irish physicians that would cover multiple issues regarding the screening and management of patients. We posted this to Irish Consultants, collected responses and then analysed the differences between ‘common practice’ and the published guidelines.

Results: 51% of consultants replied. 95% use Serum Ferritin and Transferrin Saturation as a screening tool. Preferred screening groups were those with atypical arthropathy, biochemical hepatitis and a strong family history of Hereditary Haemochromatosis. General screening is not favoured. 66% of consultants favoured a shared primary/secondary care approach. 68% suggest weekly venesection as the best option and 80% use serum Ferritin to monitor this. 78% favour venesection until Serum Ferritin is < 50 µg/L. 68% recommend six monthly checks on Serum Ferritin after venesection is completed, to monitor for re-accumulation. 75% would use Nurse Specialists. 75% would not screen the elderly, but 75% would treat them. 90% favour the donation of venesected blood; however only 50% could do this. 80% gave advice about cirrhosis. 75% felt that life assurance is irrelevant when screening. The main areas of conflict were based on tests to be performed once diagnosis was achieved and where patients were treated optimally.

Conclusions: This survey has highlighted many differences of opinion and the need for an international combined primary-secondary care protocol.

Introduction

Hereditary Haemochromatosis (H.H.) is a serious disease which untreated can cause diseases of the liver, myocardium, endocrine and rheumatologic systems. Five per cent of northern European Caucasians carry the C282Y gene. This is situated in the HFE locus on chromosome six. In Ireland homozygous frequency for C282Y gene is 1/83.[15] This is an important disease with considerable morbidity, which can be screened for. There are many national protocols in place which are incongruent with each other [7,8]. In many countries where national protocols are in place, there are still many issues with the non-uniformity of management pathways. We believe that many of the current guidelines are also out of date [6] and piecemeal in places. Many of the opinions expressed in these national protocol documents are consensus specialist group type opinions. This is because large scale trials have not been performed on many of the preferred management ideas that are used in clinical practice. Many of the guidelines are thus ‘care by opinion as opposed to ‘care by the judicious use of best evidence’. We set out here to find the views of Irish consultants on the management of this important disease.

Methods

Design of study: A questionnaire survey for all hospital consultants directly involved in the care of patients with Hereditary Haemochromatosis in the Republic of Ireland. This study was piloted with consultant physicians and hospital based G.P. trainees prior to release. The 16 questions were closed and informed by the H.A.S guidelines France, B.H.S guidelines, United Kingdom and the primary care guidelines from the Centre for Liver Disease, Mater University Hospital Dublin, Ireland.

Participants: The Irish medical directory was consulted and a list of physicians was obtained. We included all Gastroenterologists and Haematologists in
the Republic of Ireland in the study. These specialists would almost certainly care for most patients with the disease in urban areas. To get a broad spectrum of the varying policies throughout the state we also sent the questionnaire to all internal physicians in hospitals where a Gastroenterologist was not employed full-time.

**Study questionnaire:** There were 16 questions which examined all aspects of the screening and management of the disease. Fifteen of the questions required the picking of a single best answer from a list of possible choices. The choices were informed by the H.A.S (Haute Authorite de Sante) guidelines France, B.H.S (British Haematology Society) guidelines in the United Kingdom and the guidelines from the Centre for Liver Disease, Mater University Hospital Dublin, Ireland. The first question allowed the consultants to pick as many answers as they liked, this question was based around possible screening groups. Most of the respondents replied as directed but some clarified answers in the margins.

**Procedure:** The physicians replied by post. Separate response postcards allowed for anonymity.

**Data analysis:** The data was analysed in a quantitative manner with the percentage agreement amongst the consultants for any particular answer being shown.

**Results**

There was a response rate of fifty one per cent. (Number=67)

**Screening:** As a starting point the consultants were given the seven screening group options in listed in (figure 1). They were allowed to select all seven choices, if they felt that each single group was a priority screening target. Most selected a first degree relative with Hereditary Haemochromatosis as the primary target screening group. There were variable opinions on all other groups as you can see in Table 1. The screening of those greater than 80 years of age is favoured by only 25 % of consultants. The favoured tool for screening is a combined test of fasting Serum Ferritin and Transferrin Saturation together (95 % of consultants).

**Referral:** 61% consultants felt that Gastroenterology was the most suitable referral point for general practitioners. 13% felt haematology was acceptable and 26% felt uncomplicated patients should remain in primary care.

**Tests:** The decision about which tests are required to assess end-organ damage in patients diagnosed with Hereditary Haemochromatosis was a contentious issue. 47% felt testing was unnecessary unless the Ferritin level at diagnosis was > 1000µg/L .32 % suggested all patients diagnosed genetically should have a liver ultrasound scan and echocardiogram. 17% favoured a liver ultrasound scan for all diagnosed but an echocardiogram was only needed if cardiac failure was suspected. 1% recommended an echocardiogram alone if the serum liver tests and alpha foetal protein level were normal. Table 2.

**Further opinions with regard to Hereditary Haemochromatosis that were evaluated:**

1. 75% of consultants agreed with the use of nurse specialists to run venesection protocols. 90% of consultants recommend the donation of suitable venesectioned blood to the ‘blood pool ’for donation purposes but only 50 % were in a position locally to facilitate this. This programme is not accessible nationally outside of the country’s capital city.80% felt that it was necessary to give specific cirrhosis information to patients as this is the main area of morbidity. 75% would screen for this disease without informing patients about life assurance issues.

**Discussion**

**Discussion of screening group issues (Q1).**

Family screening ultimately leads to discovering the highest number of C282Y homozygotes. It is estimated that 33 % of proband siblings will be homozygotes for C282Y.[1] The second most favoured screening group was those with Serum liver function test abnormalities. In a Liver Clinic, patients with elevated iron parameters and abnormal liver tests had Hereditary Haemochromatosis 7.1% of the time.[1] Venesection certainly benefits those who have elevated Liver iron concentration without cirrhosis but if cirrhosis is present any benefit seems doubtful.[11] The third most popular screening target group was those with atypical arthralgia. Patients tested in an Arthritis clinic showed no difference in C282Y detection level from controls in the general population[1]

A recent paper however has highlighted that the supposed increased cardiovascular risk in anybody with Hereditary Haemochromatosis probably doesn’t exist. [10] The benefit of screening of those with Congestive cardiac failure is thus unclear. One study identified 5.8% patients from the Diabetic population who were Hereditary Haemochromatosis homozygotes .A recent trial however has shown that whilst detection rates of the disease in the Diabetic population is higher than control, the amount is probably less than the 5% previously shown. [2]
Another study implies that early detection and venesection doesn’t improve glycaemic control in this C282Y homozygote population.[3] A third study questions any increase in morbidity/mortality from Diabetes Mellitus in C282Y homozygotes. [14] There are huge workload and ethical issues about screening the general population for this disease. The United States preventative services task force has stated that their remains insufficient evidence to predict the impact of, or estimate the benefit from, widespread genetic screening for H.H. [1]

To summarise; It seems that the screening of first degree relatives of C282Y probands is beneficial as the yield of symptomatic disease is probably worth the effort. A similar case could be made for screening patients presenting with liver disease and those with Diabetes. The yields here however are much smaller for the screening effort involved (5-7 %). EASL guidelines questions the benefit of screening the Diabetic population.[18] A large screening effort in Rheumatology clinics will reveal some patients with Hereditary Haemochromatosis but the screening yield of patients with genetic Hereditary haemochromatosis will be small (5%). The screening of second degree relatives yields little result for much effort. General population genetic screening should be discouraged on current evidence and the benefit of screening congestive cardiac failure patients is unclear.

Irish Consultants have varied groups that they wish to target as priority screening groups and not all of this is evidence based and aligned with current guidelines.

Discussion of management issues
When looking at the question of which screening test is best, a combination approach of serum Transferrin Saturation and Serum Ferritin if favoured by most. This decision is based on sound evidence (Level A-B) [12] The evidence regarding referral, which tests are needed post diagnosis, and where is best to treat patients, is lacking. The best available advice comes from different national protocol papers. This is all Level D evidence [7,8] When discussing matters with regard to venesection protocol management issues (Table 1), any evidence to support these opinions is weak (Level C-D). The evidence largely comes from national protocols/committees [7,8]

There is however Level B evidence supporting weekly venesection, as longer intervals cannot deplete iron stores. The role of nurse specialists has not been examined to any great extent. Some national committees feel that this type of approach to patient management is a good idea.[8] Treating the elderly has however a reasonable evidence base. It seems to be safe and effective. [13]

Conclusion(s)

There seems to be much difference of opinion between consultants on the management of this disease and some of the evidence used in the suggested national protocols is weak in nature mainly due to a paucity of trials in particular management areas. There is also much heterogeneity between the various national protocols. Some of the national protocols are frankly out of date and do not even reference 1000µg/L Ferritin as a cut off for treatment and venesection [6]. It is also fair to say that there are management opinions which state that the cut-off figure of Ferritin 1000µg/L is not wise[5], but at least this issue is discussed and acknowledged.

There are current opinions, which suggest that the performance of genetic testing on patients whose serum Ferritin is less 1000µg/L with a concurrent Serum Transferrin Saturation greater than 45% is a waste of scarce health resources. The largest source of morbidity in this disease does not seem to occur when Serum Ferritin is [4,6]. There is one study which disputes this figure and states that there is a 0.03% risk of cirrhosis when the baseline Serum Ferritin is < 1000µg/L in patients with Hereditary Haemochromatosis.[5] This issue is hotly contested in the literature.[16] Many feel that giving genetic titles to people who will not progress to symptomatic disease needing treatment is foolish. This is an area which is muddy for many and has not been truthfully and definitively investigated.

More importantly It is also suggested that venesecting this same patient population group is also a fruitless activity. Even the most up to date substantial review of management issues[17], fails to answer this question whether the treatment of those C282Y homozygotes with a serum ferritin < 1000µg/L is worthwhile or not. They still suggest treating all with elevated iron parameters when we know that this is not of benefit to most with serum Ferritin < 1000µg/L.

There is even too much heterogeneity between various consultant opinions even within the same state. The main areas of confusion in our study related to the use of a venesection commencement threshold of Ferritin 1000µg/L or not, diagnostic tests on every patient or not and referral for uncomplicated patients or not.

We need an international management protocol with
the involvement of both primary and secondary care participants and possibly prior to this a multi-centre trial that would clarify some of the disputed management dilemmas. We do not believe that the current EASL guidelines answer these confusing questions and propose that more primary research needs to be done on this disease before the production of guidelines.

References

9. Crowe J ,Irish Centre for Liver Disease Primary Care Protocol. 2005
Illustrations

Illustration 1

Table 1
Table 2

<table>
<thead>
<tr>
<th>Venesection protocol management issues.</th>
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<tbody>
<tr>
<td>Where to venesect selected patients?</td>
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<tr>
<td>67% Shared care</td>
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<tr>
<td>18% G.P. only</td>
</tr>
<tr>
<td>10% Hospital only</td>
</tr>
<tr>
<td>5% Wherever service is available</td>
</tr>
<tr>
<td>How often to venesect selected patients?</td>
</tr>
<tr>
<td>68% Weekly venesection</td>
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<tr>
<td>21% Fortnightly venesection</td>
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<tr>
<td>8% Fortnightly if Serum Ferritin &lt;1000µg/L and weekly if greater than that.</td>
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<tr>
<td>3% Depends purely on patient tolerability of the venesection protocol</td>
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<tr>
<td>Parameters for monitoring progress of venesection?</td>
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<tr>
<td>Best figure for Endpoint of regular protocolled venesection?</td>
</tr>
<tr>
<td>Re-accumulation tests needed after protocolled Iron depletion is completed?</td>
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