Phlebotomy patterns in haemochromatosis patients and their contribution to the blood supply

Deborah Walkden, Krishna Badami

Abstract

Aims To determine venesection patterns in hereditary haemochromatosis (HC) patients in Christchurch, New Zealand, their contribution to the blood supply, and reasons for deferral.

Methods Review of clinical records of 412 HC patients venesected by the NZ Blood Service at least once during 2009.

Results Of 275 males and 137 females, 384 had been tested for HFE gene mutations—76% were C282Y homozygotes, 12.8%, C282Y/H63D compound heterozygous, 8.6%, either H63D homozygotes, C282Y heterozygotes or H63D heterozygotes. Small numbers had no detectable mutations, were not iron overloaded but had been venesected for isolated hyperferritinemia. 53% were donors. C282Y homozygotes required significantly more venesections than patients of other genotypes. Eligible HC patients donated 3 units/donor/year compared to 1.63/person/year by healthy donors (p<0.001). HC patients contributed 3.4% of whole blood collections in 2009. There were 212 permanent or temporary donation deferrals—common reasons were abnormal liver functions, chronic or malignant disease, or immigration from vCJD risk countries.

Conclusions HC donors donate at nearly twice the rate of healthy donors but contribute only a small amount to the blood pool. Revision of selection criteria may increase this contribution without compromising blood safety.

Hereditary haemochromatosis (HC) is an autosomal recessive disorder characterised by excessive iron absorption from the diet. In populations of northern European origin, as in Christchurch, New Zealand, most HC is due to mutations in the HFE gene on chromosome 6. In such populations, more than 85% of clinical HC cases are caused by the C282Y mutation. Most of the remainder are compound heterozygotes who have another HFE mutation such as H63D or S65C in addition to the C282Y mutation. A 1998 study showed homozygosity for C282Y in 1 in 200 of 1064 New Zealanders. Though the prevalence of these mutations in the New Zealand Caucasian population is high, biochemical evidence of iron overload is seen in only 70% of C282Y homozygotes and clinical manifestations in an even smaller proportion. Penetrance is even less marked in those with non-C282Y HFE mutations.

Factors influencing phenotypic expression are not well understood but probably involve other genetic components, blood loss, diet, and excessive alcohol consumption. Common symptoms in untreated HC cases are lethargy, arthralgias, loss of libido, and impotence. Complications of untreated iron overload include cardiac arrhythmias, diabetes mellitus, skin bronzing, cirrhosis, and hepatic carcinoma.
Venesections are a well-established, safe and effective treatment for HC. ‘De-ironing’ and maintenance of normal iron levels often requires venesections on an ongoing basis. An average of 33.9 venesections was required during the de-ironing phase in a study of over 2000 American HC patients.³

It is now accepted that HC patients can safely donate blood if they are otherwise healthy.⁴,⁵ Since they tend to donate more frequently than their non-affected counterparts, they could make a substantial contribution to the blood pool.

The New Zealand Blood Service (NZBS) provides therapeutic venesection services free of charge. Thus, there is no incentive for HC patients to obtain venesections free-of-charge by becoming blood donors, possibly concealing relevant medical information, and endangering the health of transfusion recipients in the process.

Though triggers and targets for therapeutic venesections in HC are in a state of flux, at our centre, essentially the same criteria were, and are, applied to all patients irrespective of sex, age, or genotype. Generally, we have tended to start venesections when serum ferritin levels (SF) exceed 500 mcg/L and continue treatment to keep this at less than 100 mcg/L.

NZBS allows HC patients to be blood donors provided all donor acceptability criteria are met and their liver function tests (LFT) are normal. Blood from HC patients who are not donors is either discarded or used for research purposes.

The aims of the audit were to investigate:

- To what extent HC donors contribute to the blood donor pool.
- Whether there is a difference between males and females with respect to venesection frequency, and age at initiation of venesection.
- The percentages of common genetic mutations, and venesection frequencies between genetic groups.
- The reasons for deferral from donation.

**Methods**

All HC patients, venesected at least once between 1 January 2009 and 31 December 2009 at the Christchurch centre, were included in the audit. Data—age, sex, HFE genotype, number of units venesected, the number of whole blood donations obtained, and the reasons for permanent or temporary deferral—for the 12-month period were obtained from the clinical records.

Summary statistics for sex, age, genotype, venesections, donations and deferrals were calculated. The 2 sample t-test with pooled variance was used to compare the means of continuous variables such as age, and the \( \chi^2 \) test to compare the means of categorical variables such as the numbers of males and females, and number of venesections and donations.

**Results**

We audited 412 patients (137 females and 275 males).

Data are summarised in Table 1.
Table 1. HC patients in Christchurch, 2009: demographic, venesection and blood donation characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number (donors)</th>
<th>Age mean ± SD (range)</th>
<th>Venesections (mean/patient/year)</th>
<th>Donations (mean/eligible patient/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females 137</td>
<td>Males 275</td>
<td>51.7 ± 12.7 (20–75)</td>
<td>449 (3.3)</td>
<td>186 (2.8)</td>
</tr>
<tr>
<td>67</td>
<td>152</td>
<td>50.1 ± 11.7 (18–74)</td>
<td>1111 (4.0)</td>
<td>470 (3.1)</td>
</tr>
<tr>
<td>All 412</td>
<td></td>
<td>50.6 ± 12.1 (18–75)</td>
<td>1560 (3.8)</td>
<td>656 (3.0)</td>
</tr>
</tbody>
</table>

There were significantly more males than females, and males needed significantly more venesections than females (P<0.001). However, the mean age of males and females was similar (P = 0.21) and the number of donations from males was not significantly greater than that from females (P= 0.2129).

Of 412 patients, 219 (53%) were registered as donors and they donated 656 whole blood units over the twelve month audit period averaging 3 units/eligible HC patient/year. In contrast 18,764 units were obtained from 11,485 healthy donors at our centre during the same period averaging 1.6 units/person/year (P<0.001). HC donors contributed 3.4% of the whole blood units collected in Christchurch in 2009.

Of 412 patients, 384 (93%) had been tested for HFE mutations. As expected, the majority (293, 76%) were homozygous for the C282Y mutation. Forty nine (12.8%) were C282Y/H63D compound heterozygotes, 8.6%, in total, were either heterozygous for C282Y (21), or H63D (9), or homozygous for H63D (3). A small minority (7, 1.8%) had been tested but had no detectable HFE mutation.

The average venesection rate for all HC patients combined was 3.8 units/patient/year. C282Y homozygotes required significantly more venesections than patients of other genotypes (P<0.001). There were no significant differences between the venesection rates of patients who were C282Y/H63D compound heterozygotes, C282Y or H63D heterozygotes, or H63D homozygotes (table 2).

Table 2. HC patients in Christchurch, 2009: HFE gene status and venesections

<table>
<thead>
<tr>
<th>Genetic status number (%)</th>
<th>Venesections number (mean/patient/year)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C282Y homozygote 293 (71.1)</td>
</tr>
<tr>
<td></td>
<td>Compound heterozygote 49 (11.9)</td>
</tr>
<tr>
<td></td>
<td>C282Y heterozygote 21 (5.1)</td>
</tr>
<tr>
<td></td>
<td>H63D heterozygote 9 (2.2)</td>
</tr>
<tr>
<td></td>
<td>H63D homozygote 3 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Negative for C282Y and H63D 7 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Not stated 30 (7.3)</td>
</tr>
<tr>
<td>All 412</td>
<td></td>
</tr>
</tbody>
</table>

*Average venesection rates were calculated using figures for both initial iron reducing, and maintenance phases.

178 donation deferrals were permanent (Table 3).
Table 3. HC patients in Christchurch, 2009: reasons for permanent deferral from donating

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Abnormal LFT</td>
<td>55 (30.9)</td>
</tr>
<tr>
<td>vCJD-risk*</td>
<td>40 (22.5)</td>
</tr>
<tr>
<td>Historic or current malignant disease</td>
<td>23 (12.9)</td>
</tr>
<tr>
<td>Chronic medical conditions</td>
<td>40 (22.5)</td>
</tr>
<tr>
<td>Blood borne infection risk</td>
<td>12 (6.7)</td>
</tr>
<tr>
<td>Other*</td>
<td>8 (4.5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>178</strong></td>
</tr>
</tbody>
</table>

*Residence in the UK/France/Ireland for ≥ 6 months cumulatively between 1980 and 1996
* 4 unsuitable veins, 1 faint, 1 old age, 2 personal choice.

HC patients deferred for abnormal LFT can be reinstated as donors when these normalise. Those over 75 years of age, those with cerebrovascular disease, ischaemic heart disease, or predisposition to fainting, are required to attend designated, medically-supervised clinics. Blood is not collected for donation at these clinics. Twenty one deferrals were temporary—16 on account of potential infection risk, 4 because of recent trauma or surgery, and in 1 case, due to insufficient blood collected. In 50 instances, the reason for deferral was not documented.

Discussion

The audit shows that, in our setting, 53% of HC patients were eligible to donate and they donated more frequently than non-HC donors. However they contributed only a small proportion (3.4%) of the whole blood units collected in 2009 at this centre. Leitman et al reported that 76% of their HC patients were eligible to donate blood and contributed 14% of units to the inventory. Their donors were permitted to donate with ALT levels up to 100U/L. In contrast, in another report on 16 US blood centres, only 0.4% of red cell units came from HC donors. The author attributed the low rate to the complexity of paperwork and testing associated with such donors.

Our audit included significantly more males than females, and showed that males required significantly more venesections than females. These likely reflect the natural history of HC and demonstrates the lower iron content of the female diet, and menstruation, pregnancy and lactation during the premenopausal years. Interestingly, the age range and mean age of females did not differ significantly from that of males (Table 1). This, which has also been noted in other studies, may be due to clinically mild HC being detected early in females who were tested to rule out iron deficiency as a cause of non-specific symptoms or as part of a family study following the initial diagnosis of HC in a male relative.

The proportions of subjects of each genotype in our audit was similar to that found by Leitman et al. As expected, C282Y homozygotes required more venesections than patients with other genotypes with the exception of patients homozygous for H63D but numbers were small in the latter category. Seven patients with no detectable HFE gene mutations had been diagnosed with HC based solely on high SF without documented transferrin saturation (tfs) exceeding 50%. In these patients the average venesection rate was 2.1/patient/year—considerably less than the overall rate of 3.8/patient/year. It is important to remember that a raised fasting tfs is generally
regarded an important diagnostic criterion for HFE-related HC at presentation though non-HFE HC, and some HFE-related HC may not present this way.\(^1\)

High SF with normal tfs is a common finding suggestive of conditions other than HC including inflammation, excessive alcohol consumption and the dysmetabolic syndrome.\(^9\) It is probable that the obesity epidemic is resulting in an increasing number of venesection referrals. In these cases venesections may not benefit, and possibly even harm the patient.\(^9\)

178 HC patients (43.2\%) were permanently deferred from donating. Some of these deferrals (e.g. on account of abnormal LFTs) are permanent only in the sense of being open-ended. Such patients can be reinstated as donors when these parameters return to normal. However, significant proportions of permanent deferrals are indeed truly permanent (Table 3).

About 20\% (40/199) of all deferrals amongst HC patients were because of prior residence in vCJD-risk countries compared to 0.8 \% among blood donors in general.\(^10\) This reflects the number of people of north-western European origin in Christchurch.\(^11\) In addition, it has been and continues to be, common for young New Zealanders to spend extended periods of time overseas—especially in the UK.

As expected, homozygous C282Y HC patients had higher venesection rates than those of other genotypes. The average age of male and female HC patients was similar though males were venesected significantly more often than females. HC donors donated at almost twice the rate of those without HC emphasising their value to the blood service.

Many HC donors are deferred on account of abnormal LFTs. Non-HC donors do not routinely have iron status or LFT checked and may, in fact, have abnormal results on account of undiagnosed HC, dysmetabolic syndrome, etc. The significance, to transfusion recipients, of high SF and liver enzymes in blood donors, in the absence of other abnormalities, is unclear.

A re-evaluation of current donor deferral criteria applied to HC patients is warranted. This has the potential to increase their contribution to the whole blood pool without compromising patient or blood safety.

**Competing interests:** None known.

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**References:**


