Screening for haemochromatosis- evolution of data over 20 years

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Requirements for an Acceptable Screening Program- Wilson and Jungner, Year- 2000

Important problem	**Yes**	**Suitable test**	**?**
Acceptable treatment	**Yes**	**Acceptable to population**	**?**
Facilities for diagnosis and treatment	**Can be**	**Agreed policy on who to treat**	**?**
Recognized latent stage	**Yes**	**Cost of case finding balanced v total expenditure**	**?**
Natural history understood	**Not fully**	**Continuous process of case finding**	**Can be**

Mi-Iron- A randomized patient-blinded study of true versus sham reduction of body iron in HFE related haemochromatosis with moderate iron overload

Sim Y Ong, Lyle C Gurrin, Lara Dolling, Jeanette Dixon, Amanda J Nicoll, Michelle Wolthuizen, Erica M Wood, Gregory J Anderson, Grant A Ramm, Katrina J Allen, John K Olynyk, Darrell Crawford, Louise E Ramm, Paul Gow, Simon Durant, Lawrie W Powell, Martin B Delatycki

Reduction of body iron in *HFE*-related haemochromatosis and moderate iron overload (Mi-Iron): a multicentre, participant-blinded, randomised controlled trial

Sim Y Ong, Lyle C Gurrin, Lara Dolling, Jeanette Dixon, Amanda J Nicoll, Michelle Wolthuizen, Erica M Wood, Gregory J Anderson, Grant A Ramm, Katrina J Allen, John K Olynyk, Darrell Crawford, Louise E Ramm, Paul Gow, Simon Durrant, Lawrie W Powell, Martin B Delatycki

Summary

Background The iron overload disorder hereditary haemochromatosis is most commonly caused by HFE p.Cys282Tyr homozygosity. In the absence of results from any randomised trials, current evidence is insufficient to determine whether individuals with hereditary haemochromatosis and moderately elevated serum ferritin, should undergo iron reduction treatment. This trial aimed to establish whether serum ferritin normalisation in this population improved symptoms and surrogate biomarkers.

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Do people with HH and SF >300μg/L but less than 1000μg/L need treatment?

- >1 million people in each of US and Europe and >85,000 Australians have or will get SF> 300μg/L but < 1000μg/L due to HFE p.C282Y homozygosity or p.C282Y/p.H63D compound heterozygosity

- Increasing number of commentators advising not to treat HH if SF less than 1000μg/L

Study Aim

To undertake a randomised patient-blinded trial of erythrocytapheresis compared to sham erythrocytapheresis (using plasmapheresis) in individuals who have serum ferritin (SF) > 300μg/L but <1000μg/L (defined here as moderate iron overload) due to HFE p.C282Y homozygosity and to compare the prevalence of symptoms and objective markers of disease in the two treatment arms

Erythrocytapheresis

- Blood removed
- Spun
- RBCs discarded
- Plasma returned to subject
- Plasmapheresis- opposite
- One treatment removes ~3x RBCs cf venesection
- Reduced hypovolaemia SE cf venesection because of saline replacement
- Anticoagulant can cause SE due to ↓ Ca^{++} (citrate reaction)

Blinding

Inclusion & exclusion criteria

Inclusion

1. HFE p.C282Y homozygous
2. Aged 18 years or older
3. SF above the upper limit of the normal range (300µg/L) but less than 1000µg/L with a raised TS (>ULN for testing laboratory)

Exclusion

1. HH due to other genotypes
2. Normal SF, SF >1000µg/L or raised SF in the setting of normal TS
3. Other major risk factor(s) for liver toxicity including positivity for hepatitis B or C, excess alcohol consumption (>60g/day in males and 40g/day in females), body mass index >35 (which places the individual at high risk for steatohepatitis)
4. Current or recent venesection for HH (within two years)
5. Pregnant

Outcomes

- **Fatigue-** Modified Fatigue Impact Scale (primary outcome measure)
- **QoL-** SF36 version 2
- **Depression and anxiety symptoms-** Hospital Anxiety and Depression Scale
- **Arthritis-** Arthritis Impact Measurement Scale 2 short form
- **Liver wellbeing-** Hepascore, Fibrometer, Transient elastography- Fibroscan
- **Oxidative stress-** F2 isoprostanes

SF and TS

SF	Baseline (µg/L)	End of Treatment (µg/L)
Control (n=44)	509.7 ± 23.7	478.9 ± 25.4
Treatment (n=50)	518.8 ± 24.6	203.9 ± 10.0

Mean difference in change for two groups: p <0.0001

TS	Baseline (%)	End of Treatment (%)
Control (n=44)	63.1 ± 2.7	61.7 ± 2.7
Treatment (n=50)	63.7 ± 2.3	45.4 ± 2.3

Mean difference in change for two groups : p <0.01

Modified Fatigue Impact Scale

	N	ΔControl	ΔTreatment	Adjusted Mean Difference	p-value
MFIS Total	93	-1.35 (1.74)	-6.82 (1.61)	-6.25 (2.46)	0.01
MFIS: Cognitive	94	-0.80 (0.83)	-3.90 (0.78)	-3.60 (1.16)	<0.01
MFIS: Physical	93	-0.60 (0.89)	-2.34 (0.83)	-1.93 (1.29)	0.14
MFIS: Psychosocial	94	-0.07 (0.23)	-0.58 (0.22)	-0.54 (0.33)	0.10

Other outcomes

- No significant change in SF36v2, HADS
- Significant improvement in AIMS2-SF affect ($p<0.03$)
- Significant improvements in hepascore ($p<0.05$) and plasma F_2 isoprostanes ($p<0.05$)

How successful was blinding?

"Do you think your iron level was reduced?"

	Control (n=44)	Treatment (n=50)	p-value
Yes	10 (22.7%)	10 (20%)	0.603
No	6 (13.6%)	9 (18%)	
Not sure	28 (63.6%)	29 (58%)	
Missing	0 (0%)	2 (4%)	

Improvement in control v treatment groups

- 13/14 patient reported outcome comparisons improved in treatment group more than controls (p=0.01)
- All significant changes were where treatment group improved more than controls
- No changes that were greater in the controls were significant

Conclusions

- Well blinded study
- Significant improvement in the treatment group in the MFIS total score and cognitive component and affect component of the arthritis scale
- No change in overall SF36v2 (MCS & PCS) or HADS
- Significant improvement in hepascore and isoprostanes

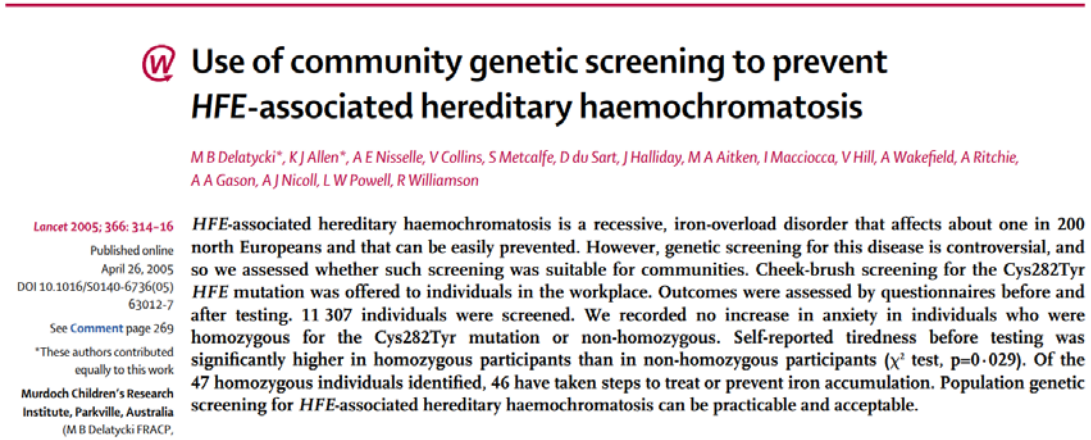
Conclusions…

- Treatment of raised SF is generally safe
- Data from this study indicates clinical benefit
- All with raised SF should have normalisation of body iron as indicated by normal SF

Haemscreen

Aims

- screen 10,000 individuals in their workplace for HFE p.C282Y
- assess whether a “worried well” population results
- assess consent in the setting of one to many education
- minimise illness due to hemochromatosis



Use of community genetic screening to prevent *HFE*-associated hereditary haemochromatosis

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HFE-associated hereditary haemochromatosis is a recessive, iron-overload disorder that affects about one in 200 north Europeans and that can be easily prevented. However, genetic screening for this disease is controversial, and so we assessed whether such screening was suitable for communities. Cheek-brush screening for the Cys282Tyr *HFE* mutation was offered to individuals in the workplace. Outcomes were assessed by questionnaires before and after testing. 11 307 individuals were screened. We recorded no increase in anxiety in individuals who were homozygous for the Cys282Tyr mutation or non-homozygous. Self-reported tiredness before testing was significantly higher in homozygous participants than in non-homozygous participants (χ^2 test, p=0·029). Of the 47 homozygous individuals identified, 46 have taken steps to treat or prevent iron accumulation. Population genetic screening for *HFE*-associated hereditary haemochromatosis can be practicable and acceptable.

Results

- 11,923 attended (11,841 eligible), 11,306 screened (53.1% female) = 95.5% uptake
- 51 p.C282Y homozygotes
- No change in SF36, STAI from pre screening to post result in p.C282Y homozygotes
- All with raised iron took steps to normalise iron indices

ironXS

- Is screening for HH in late high school students acceptable and feasible?
- HaemScreen- about 10% of eligible individuals had screening
- School is an ideal place to:
  - teach students about genetic health
  - reach a high percentage of the population with relative ease
  - empower young people to control future health

Results…

- 17,638 offered, 5757 had screening (uptake 32.6%)
- 28 p.C282Y homozygotes identified
- No change in SF36, STAI from pre screening to post result in p.C282Y homozygotes

Health economics

- De Graaff et al Appl Health Econ Health Policy 2017
- Modelled screening by genotype and by TS
- Both cost effective for males, TS screening cost effective for females
- BUT costs for genotyping excessive

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Acceptable treatment	**Yes**	**Acceptable to population**	**Yes**
Facilities for diagnosis and treatment	**Can be**	**Agreed policy on who to treat**	**Yes**
Recognized latent stage	**Yes**	**Cost of case finding balanced v total expenditure**	**Yes**
Natural history understood	**Yes**	**Continuous process of case finding**	**Can be**

Conclusion

- The case for screening for hemochromatosis is increasingly strong. There is much more data on:
  - Natural history, especially from UKB
  - Treatment response: RCT in moderate iron overload
  - Response to screening

- When and how?
  - Opportunistic through primary health care, people having genomic testing for another reason
  - Stand alone- high school, home testing (akin to bowel cancer screening)
  - At time of reproductive carrier screening
  - Secondary prevention – clinical screening re arthritis/osteoporosis, chronic pain, diabetes, etc