case study providing interesting but preliminary results.

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References

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Haemochromatosis and non-hepatic malignancy

Sir,

We thank Dr Das for his interest in our recent review.1 He highlights the high risk of non-hepatic malignancies in hereditary haemochromatosis (HH).2

Figure 1. Body weight, differences in an angle paradigm, and EEG theta (3.5 Hz–7.5 Hz) activity of patient A.B. during 14 months. Upper part: Pattern of body weight (solid line, ordinate on the left side) and deviations of angle between nominal and reproduced angles in the angle paradigm5 at five points in time (t0–t4) (grey bars, ordinate on the right side). The red bar indicates the time during which the patient used the diving suit (for one hour three times per day). Small yellow bars indicate an episode of a common cold. Note that highest weight and smallest differences between nominal and reproduced values of angles were observed at the second measurement (t2), i.e. during the treatment. Lower part: Power-maps of background EEG theta activity with eyes closed at five points in time (t0–t4). A strong activation of the right hemisphere could be observed at (t2), i.e. during the treatment. The patient wearing the diving suit (at t0) is depicted on the right.
While the increased prevalence of hepatocellular cancer in HH is not in debate, controversy does surround the rate of non-hepatic malignancy in HH.

Some studies that suggested a higher incidence were limited in design or clearly defined outcome measures. In one study of 71 patients with HH, an 8.4% rate of non-hepatic cancer was noted in 7 years (only six cases) of follow-up, with no claim made as to statistical significance. In a study quoted by Dr Das, Nelson et al. showed a statistically significant increased risk of gastric and colorectal cancer, but their primary endpoints included many different types of cancer, some showing no increased risk compared to controls. Further, in the study by Fracanzani et al., which showed a relative risk of 1.8, suggesting a definite trend towards an increased risk, the results did not reach statistical significance (95%CI 0.8–4). There were 20 cases of non-hepatic malignancy in this study, with nine in the control group, but the increased numbers were in the colon, bladder and lung, organs not known to accumulate excess iron in HH.

Since increased iron stores alone have not been shown to be pre-malignant in recent studies, it has been suggested that interplay between genetic factors in HH could be implicated in the development of malignancy.

A recently published study compared the frequencies of HFE C282Y and H63D alleles and associated odds ratios in 100 consecutive unrelated White adults with malignancy to those in 318 controls in a community-based oncology practice. The frequencies of the C282Y and H63D alleles were similar to those in the general population, leading investigators to conclude that C282Y and H63D were not associated with an increased cancer risk. The odds ratios did suggest, however, that the development of specific types of malignancy may relate to the inheritance of the HFE gene. In a population-based study of 1847 heterozygous individuals and their 5973 first-degree relatives, patients with HH had a 20-fold increased risk of liver cancers, but with an almost unaltered risk of all other cancers (95%CI 1–1.4), including gastrointestinal cancers. The overall risk of cancer in first-degree relatives did not appear to be increased.

That non-HFE genetic factors may interfere with the risk of developing cancers suggests exciting implications for basic science research. For example, polymorphisms of tumour necrosis factor affect the expression and severity of liver damage in patients with HH, with a lower prevalence of cirrhosis noted in patients with TNF-α polymorphisms than in those without.

Iron overload may be carcinogenic. On the basis of the current evidence, however, the risk of non-hepatic malignancy in HH cannot unequivocally be stated to be higher than in matched controls. There is a clear need of further information from more and better-designed studies that incorporate careful follow-up of identified HH patients and matched controls.

The association of extra-hepatic malignancy in HH is intriguing, raising as many questions as it seems to answer. We commend Dr Das on the splendid service he has set up at his hospital, and believe that it is the work of similarly dedicated clinicians that will form the basis of the much-needed evidence to unravel this mystery.

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References

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Bilateral adrenal haemorrhage and coeliac disease

Sir,

Granel et al. describe an interesting case of bilateral adrenal haemorrhage in a patient with