SHORT REPORT

Primary liver cancer in two sisters in Holland with intermittent acute porphyria

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Two sisters living in Holland, with a niece now living in South Africa, were reported in 1958 to have inherited intermittent acute porphyria (IAP). In 1994 both sisters died from primary liver cancer. Other reports have also noted an increased mortality from carcinoma of the liver in porphyrics. Porphyria variegata has a high prevalence in white and coloured South Africans, and it would be relatively easy to ascertain whether those who have inherited the gene for this disorder, in South Africa, have a higher than reported mortality from liver cancer. If they do, consideration should be given to ways to reduce their risk of developing and dying from this cancer.

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In 1958, a study was undertaken in Holland and Sweden to ascertain whether the porphyria which had been inherited by a large number of white South Africans[1] was the same disorder as that described by Waldenström in Sweden, intermittent acute porphyria (IAP).[2] In both the South African type of porphyria and in IAP, acute attacks followed the use of drugs, in particular barbiturates and sulphonamides, and both are Mendelian-dominant disorders.

During the 1958 study, two families were seen in Holland (by courtesy of Professor P Formijne and Willhelmina Gasthüis, Amsterdam), some of whose members had already suffered from attacks of acute porphyria. In one family the disorder was similar to that which occurred in South Africa; acute attacks followed the taking of barbiturates, the exposed skin abraded and blistered easily, and patients' stool porphyrin content was high but porphobilinogen was only detected in the urine during an acute attack. In the second family, acute attacks followed

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the use of barbiturates but there was no history of a sensitive skin that abraded easily, stool porphyrin content was normal and porphobilinogen was present in the urine both in the acute and quiescent stages, according to Ehrlich's aldehyde test (Fig. 1).[1]

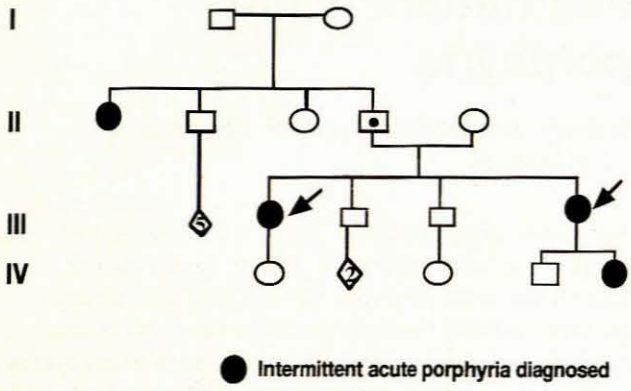

Fig. 1. Intermittent acute porphyria in a family in Holland.

The elder sister in the Netherlands IAP family was born in 1922. In 1951, aged 28, she became acutely ill with severe pain in her back and legs after taking barbiturate sleeping tablets. She was hospitalised for 6 weeks but no diagnosis was made. In 1953 she complained of abdominal pain and underwent a laparotomy; anaesthesia was induced by thiopentone anaesthetic. A few days later she developed symptoms of apparent hysteria and complained of severe pain in her abdomen, back and legs. She became paralysed and was found to have peripheral neuritis, and was diagnosed as having an acute attack of IAP. She was hospitalised for 3 months. After this attack she took no barbiturates and remained well.

Her sister, born in 1927, had four attacks of acute porphyria, the first when she was 18 years old in 1946 and the last in 1953. Each attack followed the taking of barbiturate sleeping tablets. IAP was diagnosed when she developed weakness in her limbs during her last attack. In 1953 she stopped taking barbiturates and had no further attacks of acute porphyria. In 1973 her right breast was removed because of mammary carcinoma, but after this there was no evidence of any recurrence.

The study undertaken in Holland and Sweden in 1958 showed that the South African type of porphyria was a different disorder to IAP. Because it manifested itself in a variety of forms, Dean and Barnes proposed that it be named porphyria variegata.[1]

In 1994 a nursing sister (M F) living in South Africa, a niece of the two aunts, informed one of us (G D) that both her aunts with IAP had developed primary liver cancer. A few months earlier the younger sister had complained of abdominal discomfort and a tender liver; a needle biopsy of the liver revealed primary liver cancer cells. This was followed by a laparotomy which showed that the neoplasm was not resectable and also that she had liver cirrhosis. About the same time her older sister complained of abdominal discomfort, and hearing of her sister's illness suspected that she might be similarly affected. Ultrasound of her liver showed two lesions in the left lobe consistent with tumour and needle biopsy revealed a highly differentiated primary liver carcinoma.

Discussion

In 1984, Lithner and Wetterberg described an increased risk of primary carcinoma of the liver, sometimes associated with cirrhosis, in those who had inherited IAP.[3] Primary liver cancer has also been described once before in two sisters with IAP.[4] Kauppinen and Mustajoki[5] studied the eventual cause of death in 76 patients (40 men and 36 women) with IAP, of whom 7 died with hepatocellular carcinoma. They also studied 20 deaths in 8 men and 12 women who had inherited porphyria variegata; 1 among them died of primary liver cancer.[5] An increased risk of hepatic carcinoma also occurs in porphyria cutanea tarda.[6]

In the 1950s and 1960s there was a high incidence of acute porphyria in South Africa in those who had inherited porphyria variegata, the acute attacks generally occurring after the taking of barbiturate sedatives or after anaesthesia induced by thiopentone.[7] Attacks of acute porphyria in South Africa have now become relatively uncommon because barbiturates have largely been replaced by tranquillisers and because many of the South African porphyric families are now aware of the danger of taking certain drugs. In 1996 the gene responsible for porphyria variegata in South Africa was located on chromosome 1 (R59W).[8]

More than 20 000 white and coloured South Africans have inherited porphyria variegata from one ancestor who married at the Cape in 1688.[7] It is important therefore to ascertain the risk of primary carcinoma of the liver in those who have inherited porphyria variegata in South Africa, only a minority of whom may have had acute porphyria. Many South African porphyric families are well documented, e.g. by the MRC Porphyria Research Unit in Cape Town and from the records held by the SAIMR in Port Elizabeth. It would be relatively easy to ascertain the eventual cause of death of those known to have the gene for porphyria variegata.

If those who have inherited the gene for porphyria variegata have a high risk of developing cirrhosis of the liver and hepatic carcinoma, it is important that they take particular care to avoid certain drugs and chemical substances that may damage the liver, perhaps including alcohol. Doctors should then have a high level of suspicion of the possibility of primary liver cancer in those who have inherited this gene.

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