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CLINICAL CASE REPORT

John's story - living with hereditary haemochromatosis

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ABSTRACT:

Iron can accumulate in the body due to several causes, resulting in iron overload syndrome. The most common cause is hereditary haemochromatosis (HH), a genetic disorder triggered by inactivation of the iron hormone hepcidin, which results in hyperferraemia and excessive tissue iron deposition. Other causes include repeated blood transfusion, iron-loading anaemias and some chronic liver diseases. Left undiagnosed, HH can cause significant damage to the liver, heart, pancreas and joints, because excess iron is toxic. This also increases the risk of hepatocellular carcinoma, especially in those with cirrhosis of the liver, with an estimate of 1 in 10 HH patients affected. The risk of developing type 2 diabetes is increased by 2.5–7.1 times compared with non-diabetic patients. Haemochromatosis is usually considered when elevated serum ferritin and transferrin saturation levels are found. Ferritin in excess of 300 ng/mL usually indicates iron overload. Genetic testing can identify the two most common mutations in the *HFE* gene – a positive result confirms the diagnosis of haemochromatosis – but there are also rare forms of the disease unrelated to *HFE* mutations. Liver biopsy can be used to ascertain iron accumulation and histological presence of fibrosis (cirrhosis). Assessment of the hepatic iron index is considered the gold standard for diagnosis of haemochromatosis. Magnetic resonance imaging has been used as a non-invasive alternative to accurately estimate iron deposition levels in the liver, heart, joints and pituitary gland. Population screening is not recommended; however, family members of identified people should be screened to determine their phenotypic or carrier potential. Early diagnosis enables preventative measures to be commenced.

Routine treatment is by regular venesection of 500 mL of whole blood per session. An initiation phase of weekly or twice-weekly venesection is common until serum ferritin (SF) is reduced to normal. When SF and other markers are within normal range, regular venesections are usually scheduled 1–3 months apart, depending on the underlying cause and SF response. Dietary iron including red meat and fortified foods such as cereals should be avoided. Vitamin C promotes iron absorption, and supplementation should be avoided, as should alcohol, which can increase the risk of concomitant liver disease.

John's story outlines a typical journey through diagnosis, treatment and care during HH while living on Arran, an island off the coast of Scotland. Subsequently, John developed hepatocellular carcinoma, and his treatment and palliative care are described.

We wrote this article to give the reader an insight to this silent disorder and the value of recognising the signs and symptoms for early diagnosis and subsequent treatment.

Keywords:

cirrhosis, hepatocellular carcinoma, hereditary haemochromatosis, palliative care, Scotland, type 2 diabetes.

FULL ARTICLE:

Introduction

Hereditary haemochromatosis (HH) is a genetic disorder that causes the body to absorb too much iron. If untreated, iron can build up over many years and cause organ damage[1]. Individuals with HH tend to be identified at a young age based on abnormalities found on routine blood tests, or testing after a family member has been diagnosed[2]. A higher incidence of HH is seen in individuals of Celtic and Scandinavian origin[3]. It is estimated that 10% of the population are carriers of the C282Y mutation on the *HFE* gene associated with HLA-A3, and 1% will have HH[2].

Symptoms associated with haemochromatosis are as follows. They are not usually noticed until adulthood, typically after the age of 40 years[2]:

- arthritis in the joints, particularly in the knuckles of the second and third fingers[2]
- chronic lethargy and tiredness
- shortness of breath
- irregular heart rhythm or enlarged heart
- diabetes
- changes in skin colour – bronzed/sunburnt look
- joint and bone pain[2]
- abdominal pain – cirrhosis of the liver
- testicular failure.

The organs most commonly affected are the liver, heart and endocrine glands. Men with the disease are 24 times more likely to experience symptoms than affected women[4]. There is a lower incidence in women due to natural blood loss during menstruation. Routine treatment is by regularly venesecting 500 mL of whole blood per session.

John's story

John was born in 1955 in Langholm, Scotland to Tom, a local builder, and Jessie, a nurse at the local hospital. At birth John was jaundiced, from which he made a good recovery. He led an uneventful childhood with no serious illness. At school, John had undiagnosed dyslexia and his reduced academic performance was attributed to laziness. John was sent to boarding school to try and

improve his academic ability, without success. During this time, he became interested in farm animals, and when missing from school could normally be found at a nearby farm. He left school at the age of 16 years with no academic qualifications, but he had remarkable practical skills. Initially he worked on a farm as an apprentice to become a shepherd, achieving distinctions in City & Guilds for the care of sheep and cattle. He remained fit, and typically walked 22 miles a day in his work.

John moved to Arran, an island off the coast of Scotland, at the age of 19 years to manage a farm and this was followed by a succession of similar practical occupations. John also became involved in many voluntary organisations and made many friends. He did not smoke and he drank in moderation. His mother died from liver cirrhosis (of unknown cause) and his father's death was caused by an aortic aneurysm. Notably, his father had a noticeable skin 'tan'.

In 1994, John and I (coauthor Julia Graham) met by chance. He was working as a heavy goods driver for the local haulage company. He had gout and was hobbling about the yard. I made a joke about drinking too much port. He replied with 'hmphh – a typical nursing comment, that'. We married in 1996, with John working in the newly opened distillery and me as a community nurse.

Before the diagnosis of haemochromatosis

About 2 years after we met, John started experiencing bouts of cramp in his calves and thighs, and these episodes became more frequent. He had several episodes of gout and initially commenced indomethacin but this caused indigestion. He was commenced on allopurinol (during a symptom-free period), but gout persisted. He woke up one morning with a terrible headache and was found to have hypertension. We attributed this to stress and it returned to normal within a week without treatment.

The distillery work involved cleaning out stills with caustic soda. John's work clothes were always full of pin-holes, where the drips had been spilt. One day he complained of a burning sensation in his knee and a small swelling had developed. He wrongly assumed it was to do with caustic soda. Gout was diagnosed by his general practitioner (GP) a few days later. Another week later and he was in agony and had 'flu-like symptoms. Fluid and pus were aspirated: John had developed septic arthritis. With antibiotics and bed rest he recovered and the episode was forgotten.

Later, he developed pain in his hands, particularly his second and third fingers. He attributed this to working outside in the cold for many years. He was always clenching and unclenching his hands `to loosen the joints`. He didn't suffer sunburn but tanned easily.

In 2001, John started complaining of feeling tired and listless, and had lost weight, but we thought this was due to a difficult shift pattern at work and renovating our house. He had many interests including volunteering for the coastguard, maintaining our yacht, scuba diving and walking our dog. I came home from work one day and he was supposed to have cooked the dinner. Instead he had fallen asleep on the settee and was clearly unwell. I checked his blood sugar and it was 23 mmol/L. He had been drinking more water than usual but neither of us had noticed as the weather had been hot. There was no family history of diabetes and John had never been overweight. Type 2 diabetes was subsequently diagnosed and treatment commenced. He was prescribed gliclazide and metformin and referred to a dietician. He was seen regularly by his GP who was concerned that his HbA1C and liver function tests remained elevate despite treatment. More diabetes medication was prescribed ,with little effect.

Definitive diagnosis

In 2004, a consultant endocrinologist came to Arran to give a lecture on diabetes, which I attended. Reflecting on his lecture, I requested that John be referred to the diabetes clinic. After 3 months, he saw the consultant endocrinologist and the diabetic specialist nurse. He answered one question proudly: he never got sunburnt but tanned easily. We left the clinic with the words 'I think I know what is wrong with you but I need to do some more blood tests and a liver scan'.

A couple of weeks later, John received an appointment for a heart scan – I thought it was a mix-up but on contacting the clinic it transpired that this test had been added as John now had a definitive diagnosis: haemochromatosis. Neither of us had heard of the condition, and the consultant explained in detail what it was and the next stages of investigation.

John was referred to the gastroenterologist who was to treat John for the rest of his life. John's heart scan was normal but his liver scan confirmed an enlarged liver – he would need a liver biopsy. His serum ferritin (SF) level was grossly elevated and he would require venesection weekly at Crosshouse Hospital. Given the travelling difficulties, it was agreed that subsequent venesections could be provided on Arran, and he would keep in close contact with John's GP. John's immediate family would need to be screened for haemochromatosis.

John had extensive liver cirrhosis and we were subsequently told what this could entail as the condition progressed: abdominal pain and distension, oedematous legs and coughing up blood – all of which would require an urgent GP appointment.

Treatment

John's weekly venesection did not bring his SF levels down so frequency was increased to twice weekly. At this time, all the distillers were made redundant from the distillery. John started a grass cutting service in nearby Lochranza. As disappointed as he was over the redundancy, it proved to be the best thing that could have happened to him. Two afternoons a week were required for venesection; after each session he was straight out the door and back to work!

One of the GPs was – at this time – able to provide ultrasound scanning. John's liver was scanned at 6-monthly intervals. Our lives settled back to normal and John was seen annually by both of his consultants. When John's diabetes control started to deteriorate around 2006–2007 he commenced insulin.

John never suffered from gout again but his thigh cramps worsened as the years went by. His hands and knee joints became more painful. Analgesia was prescribed: tramadol and diclofenac. We enjoyed life to the full and John continued to volunteer for the coastguard and first responders. In 2008, he was thrilled to get a relief/on-call position at the Arran War Memorial Hospital, a job he loved. In March 2013, he became heavily involved with a snow storm of unprecedented severity that hit Arran, and so he worked 18 hours a day between the coastguard and the hospital for 5 days with no ill effects.

Decline in health, 2013–2014

In January 2014, John started to feel unwell. His stools were very pale in colour and the whites of his eyes developed a yellow tinge: icterus. After attending an emergency GP appointment, it was confirmed that his liver function tests had worsened significantly. John decided to stop all his medication, with the exception of insulin. Ultrasound found no significant changes to his liver. His bloods were taken every couple of days and within days they returned to normal. He was also scanned at Crosshouse Hospital and no changes were noted in his liver. I wondered if naproxen had caused hepatoxicity. He was recommenced on diclofenac. This 'blip' took a lot out of John and he required 5 weeks off work, returning to work just a few hours a day and his share of on call for the hospital. He was usually seen in April by the gastroenterologist, but this particular year the appointment was postponed until August.

John was nominated to carry the Queen's Baton for the Commonwealth Games for his voluntary services and for the amount of help he gave local people. He was so proud and honoured to carry it on 15 July 2014 and he got the only bit in Saltcoats that was uphill; despite this, he ran every step of the way. On our 18th wedding anniversary, on 17 August 2014, John complained of right sided abdominal pain and only had half portions of food on our celebratory night out. His appointment with the gastroenterologist was 2 days later and I decided to go with him. We went through everything that had happened since January and the bloods remained within normal range. The consultant said 'I would like to do one more blood test. If these are OK I will see you next year'. The next day our GP rang us at home and said he wanted to see both of us the following afternoon. I knew that this was going to be bad news.

Hepatocellular carcinoma

Our GP confirmed that John's clinic blood test was indicative of liver cancer. Ten years after being diagnosed with haemochromatosis he had developed hepatocellular carcinoma. Iron overload increases the risk of hepatocellular carcinoma, especially in those with cirrhosis of the liver[5]. Significant liver problems occur in about 1 in 10 patients[4]. The risk is also increased in type 2 diabetes from 2.5 to 7.1 times that of non-diabetic patients[6,7]. John had both risk factors.

Initially the only symptom that John experienced was abdominal pain. We were both in denial and complete shock. I had just started phased retirement from my district nursing staff nurse post of 23 years. The consultant said to us 'most people want to know how long they have left.' We replied in unison that we did not want to know and John said he was going to make a bucket list of things for us to do. John was on call for the next 4 nights for the hospital and I was rostered to work Friday and the weekend. John refused to ring in sick and I went to work as usual. We spent the weekend telling his family and customers that he had cancer. His sister, partner and nieces were in disbelief. On Saturday night, he was in considerable pain – I was stunned he had gone from carrying the baton, appearing really well, to cancer in just a month. His pain settled with short-acting morphine. He had the scan and the results were sent to the Edinburgh Liver Unit to discuss treatment with the multidisciplinary team. We both had time off work, me because he needed me to be there for him.

Terminal diagnosis

We had a week to wait for the results and a long-term plan. Then there was more bad news: John's scan had identified a 6 cm tumour resting near his portal vein. He was referred to the Beatson Cancer Hospital.

John's GP was going on a sabbatical to New Zealand for 6 months, which was a blow for John. John requested David (coauthor of this article) to be his named doctor: he had spent hours with him in the snow storm of 2013 and other emergency service incidents on Arran. They had great respect for each other. On Arran, there is always a named doctor to care for cancer and end-of-life patients, who will visit even if they are not on call, bypassing NHS 24, Scotland's national telehealth and telecare organisation.

John had an amazing outlook on his fate and we started to sort out his/our affairs. We updated our wills and arranged for me to act as power of attorney. He cleaned his boat to sell, and two friends helped him to sail it to the mainland. I stood on the end of the Lochranza pontoon howling with emotion as it turned the corner out of sight. He sorted out his diving gear to give to a friend and washed our 30-year-old camper van. His grass and hedge cutting customers were organised with new help. Many of his friends came to see him and his sister and partner came to stay, and the dog sneaked up on the bed with him.

We got an appointment a week later at the Beatson Oncology Centre, a depressing visit which resulted in the news that there was no suitable treatment available for him in Scotland. There was a new treatment available in England. The consultant advised that he could apply for it to be made available for John. We saw the palliative nurse at the same visit.

My colleagues organised a retirement party at the hospital to which John came with me. We came home to our neighbours' secret wedding.

I phoned the Beatson to advise that John wanted to go for the trial and he received an appointment to be assessed at the trials clinic. Three patients every 3 weeks were being recruited and John was suitable, but had just missed the third slot. We would be called

when the next slot was available. He was disappointed so we decided to spend some time away. This was to be our last holiday together. David came up to the house to see us on our return and spent considerable time with John, having been in touch with his gastroenterologist. I kept in touch with the community nursing service with progress. John was becoming more noticeably frail and David kept in touch with regular phone consultations and house visits.

We attended the launch of the new lifeboat in October 2014. John had completed 12 years as Royal National Lifeboat Institution crew/helmsman. This was to be his last social trip out. His appetite was poor and he started to drink less water. He was more reliant on morphine.

Palliative care

On 30 October 2014, I noticed that John was slightly jaundiced and rang David. Bloods were taken and the following day David rang us to say that he was to go in to Crosshouse Hospital as an emergency admission for assessment and another scan. He spent 5 days in hospital, and his scan showed further deterioration. Palliative care was discussed with us, and David liaised with John's consultant. John was discharged from hospital on 5 November 2014, a day early because the weather forecast meant it was unlikely that the ferry would sail. We were sent home with new medication to relieve his symptoms. On the ferry coming home John developed intractable hiccups, something we both found distressing. Haloperidol was tried but had no effect, but baclofen worked within hours. His appetite was very poor and his fluid intake deteriorated over the weekend. He was still up and about, but in the evening of Monday 10 November he vomited a large blood clot. He pleaded with me not to ring David as he did not want to be admitted to hospital. David was not on duty, but came up and spent time with John on his own. 'Just in case' medication was prescribed including for a syringe driver if needed.

On 12 November, three of John's colleagues from the hospital came up to see him after work. John insisted on getting up; we had a laugh with them and John told them in great depth about our 5 days away. After they had gone, John proceeded to eat a roast dinner. This was to be the last time he ever came down the stairs. I requested district nursing help. He was on a syringe driver for 2 days and passed away peacefully with family, friends and his dog present on 17 November 2014 at the age of 59 years.

The Beatson Hospital consultant rang the next day to say he had won John's appeal to start the trial medication.

Conclusion

Haemochromatosis is a silent hereditary disorder which is asymptomatic until adult life. Serum iron concentration can build up very slowly over many years. Because of a relatively late diagnosis, John presented with established signs and symptoms affecting the pancreas, liver and joints.

John and I had not heard of the disorder and I am sure many health professionals have not seen a case of haemochromatosis. Because of the severe sequelae of this disorder, early diagnosis is important. Early preventative measures are effective in preventing the sequelae that John experienced, along with greater life expectancy.

John's parents must have both been carriers of the disorder – his mother's death was likely caused by liver cancer and his father had easily bronzed skin.

In John's last 3 months, he knew he was dying but was so dignified in the way he handled the disappointment of there being no treatment available for him in Scotland. It has been possible to write his story, because he kept a log of the events of his health.

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