CASE REPORT

Hepatocellular carcinoma in a young man with resting and postural tremors

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md0u92dd@liv.ac.uk**SUMMARY**

A 25-year-old man who was normally fit and well, presented with a 2-year history of progressively worsening tremor. His tremor was generalised, affecting head, neck and all four limbs. One of the patient's brothers had suffered from similar problems, but never sought medical attention. Examination revealed a generalised tremor, of greater amplitude on the patient's left side, which increased in its amplitude upon exertion. Slit-lamp examination revealed bilateral Kayser-Fleischer rings and serum caeruloplasmin was found to be low, while 24 h urinary copper excretion was elevated. A diagnosis of Wilson's disease was made and an abdominal ultrasound was performed, revealing evidence of portal hypertension and a hyperechoic hepatic nodule, later confirmed to be hepatocellular carcinoma. The patient underwent partial hepatic resection and was started on D-penicillamine.

BACKGROUND

Hepatolenticular degeneration (Wilson's disease) is a rare autosomal recessive disorder of copper transport, with a worldwide prevalence of around 1 in 30 000.¹ Mutations within the ATP7B protein result in defective incorporation of copper into apocaeruloplasmin, shortening the half life (and thus plasma levels) of the resulting caeruloplasmin²⁻³; consequently, cytoplasmic copper binding proteins become supersaturated, leading to ion spillage and resultant injury of hepatocytes. As an added blow, excretion of copper into bile is also affected,³ leading to elevated blood levels and consequent injury to other cell types, particularly those of the central nervous system.² Classically, the presentation is that of cirrhosis allied to neurological or psychiatric symptoms⁴; the diagnosis is often missed or delayed, so that a high index of clinical suspicion is needed.⁴ The following is an account of a patient who was seen during an elective in Lahore General Hospital, Pakistan.

CASE PRESENTATION

A 25-year-old right-handed man who worked as a filing assistant, presented to neurosurgery outpatients with a tremor. He first noticed the tremor in his left hand 2 years ago, but it had since progressed to become generalised, interfering with his ability to write and self-care. The patient also complained of symptoms of excessive lethargy and problems with his speech, specifically of those around him finding it increasingly difficult to understand him. One of the patient's brothers had suffered from a similar tremor and was now deceased.

Further questioning revealed that the patient's parents were first cousins. The remainder of the history was unremarkable. Examination revealed a young, titubating and lethargic-looking man, with a generalised, high-frequency tremor, affecting head, neck and all four limbs; it was of a greater amplitude on his left side and appeared to increase in amplitude when the patient was asked to write a sentence. The patient's speech was dysarthric, of a reduced volume (hypophonia) and hoarse. The remainder of the neurological examination was normal.

INVESTIGATIONS

An ophthalmologist was consulted for slit-lamp examination, which revealed bilateral Kayser-Fleischer rings (see figure 1). Serum caeruloplasmin was found to be significantly decreased (0.08 g/L) and 24 h urinary copper excretion was elevated. The patient's liver enzymes were within normal range and he was screened for hepatitis, with serology returning a negative HbSAg and anti-HCV. An abdominal ultrasound was performed, revealing mild splenomegaly (14.3 cm×6.1 cm) and a coarse, 13.7 cm liver, with a rounded, hyperechoic lesion, measuring 11×13 mm, in segment 8. After consideration of the differential for this lesion, blood tests including white cell count (WCC) and α -fetoprotein (AFP) were arranged, as

Figure 1 Bilateral Kayser-Fleischer rings. These represent copper deposition in Descemet's membrane.

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was an abdominal CT scan to further define its morphology. WCC was found to be within normal limits, but AFP was elevated (150 ng/mL). The CT scan revealed an irregular hepatic nodule.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the neurological manifestations of Wilson's disease (WD) includes young-onset Parkinson's disease, benign essential tremor and generalised dystonias. Clinically, the presence of Kayser-Fleischer rings helps to distinguish WD from these disorders.

TREATMENT

A diagnosis of WD was made on clinical grounds and the patient was referred to a hepatobiliary surgeon for his liver lesion. An initial biopsy revealed histology consistent with a primary hepatocellular carcinoma. A hepatic resection was carried out, and the patient was started on D-penicillamine thereafter.

OUTCOME AND FOLLOW-UP

At 1-month postoperatively, the patient was well and his tremor appeared to have improved somewhat.

DISCUSSION

Neurological manifestations of WD are more common among male patients.⁵ Common symptoms include: dysarthria, dystonia, tremor, parkinsonian symptoms and rarely, cerebellar symptoms.⁴ Of these, dysarthria is frequently reported as the most common neurological symptom.^{4 6 7} Dysarthria can be of virtually any type; in this case, the combination of speech abnormalities resembled a parkinsonian phenotype.

Tremor is reported to occur in 22–55% of patients with WD.⁸ This can be of the postural, intention or rest type, though the latter is usually accompanied by one of the other types, rarely presenting in isolation.⁴ Classically, WD is associated with a 'wing-beating' postural tremor, so-called because when patients abduct their arms to 90°, a proximal, high-amplitude tremor may produce arm oscillations which remind the examiner of a bird flapping its wings.⁸ Although a useful vignette, a non-wing beating postural tremor is in fact the subtype most frequently observed in patients.⁴ In this case, it was difficult to differentiate the postural tremor from the resting tremor, resulting in what appeared to be a continuous tremor. However, when the patient was asked to write, the amplitude of the oscillations increased dramatically, pointing to two distinct tremor types. The postural tremor closely resembled benign essential tremor, except its asymmetrical nature and sparing of voice quality, consistent with other descriptions of the postural tremor of WD.^{4 6}

Hepatocellular carcinoma (HCC) is a rare and controversial entity in WD. One large series investigating this link found cases only after a period of at least 10 years after diagnosis; age, among other factors, could have confounded these results and the authors failed to include a control group for comparison.⁹ Nevertheless, from a purely scientific perspective, the association is predictable.

Thattil *et al*¹⁰ have summarised the literature in this area, with only seven previously reported cases having been diagnosed with HCC upon, or soon after, diagnosis. In mice models, hepatic copper accumulation is accompanied by iron, facilitating DNA breaks and sustaining free radical formation.¹¹ This point is important as D-penicillamine itself can lead to increased levels of iron in hepatocytes, facilitating oxidative damage to hepatocytes.¹⁰ No trials have yet assessed the effect

of medication alteration on the incidence of HCC among patients with WD.

Carcinogenesis itself is probably potentiated by the activation of pathways enabling angiogenesis, ensuring tumour survival.¹² Angiogenesis is facilitated by vascular endothelial growth factor (VEGF), which in turn is transcribed by a complex including a subunit of hypoxia-inducible factor 1 (HIF-1).¹² Usually, VEGF transcription takes place in states of hypoxia, though copper is able to sustain this process even under normoxic conditions¹³; it prevents degradation of the HIF-1 subunit and plays an essential part in the formation of the VEGF transcribing complex.^{12 13} Thus, a potential association between WD and HCC is biologically sound.

In summary, physicians dealing with patients with WD should be alert to the possibility of hepatic malignancy.

Learning points

- ▶ Wilson's disease should be considered in young patients presenting with new-onset tremors.
- ▶ Resting and postural tremors may be difficult to distinguish in patients with movement disorders.
- ▶ Physicians dealing with patients with Wilson's disease should be alert to the possibility of hepatocellular carcinoma.

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Contributors MW wrote up the case and carried out the literature review. AHV was the doctor involved with patient management and directed treatment of the patient during the patient's stay at the neurosurgery unit. He checked over a summary of this case (and several others).

Competing interests None.

Patient consent Obtained.

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