Clozapine-induced hepatitis confirmed by rechallenge

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Clozapine is an atypical antipsychotic that holds a unique role in the management of treatment-resistant schizophrenia. Well known side-effects include agranulocytosis and myocarditis but associated hepatic disorders are less familiar and listed under ‘rare or very rare’ by the British National Formulary. However, a transient elevation of transaminases has been estimated to affect up to 50% of patients treated with clozapine. This article describes a patient with minimally elevated LFTs who subsequently developed symptomatic hepatitis following the initiation of clozapine therapy.

A 43-year-old South Asian man had a long-standing diagnosis of paranoid schizophrenia. He was resident in a specialist mental health nursing home and was prescribed olanzapine 20mg, risperidone 6mg and risperidone long-acting injection 50mg fortnightly. Evidence for the use of high-dose antipsychotic therapy is lacking and it is clearly associated with more frequent and severe side-effects. Our patient had first presented to mental health services in his late teenage years and subsequently had multiple admissions. He was discharged from a three-year inpatient rehabilitation stay on the above combination of medication. Functionally and symptomatically he was the best he had been in years although still experiencing positive (auditory hallucinations and persecutory delusions) and negative (low mood and a lack of motivation) symptoms. He had previously declined clozapine, but following an exacerbation of his symptoms he wished to start it.

His medical history included recent diagnoses of type 2 diabetes mellitus and hypercholesterolaemia for which he was prescribed metformin and simvastatin. Baseline bloods, including full blood count, urea and electrolytes plus liver function tests (LFTs), were unremarkable besides a slightly raised alanine aminotransaminase (ALT) of 86U/L (normal range 10–50U/L). However, his ALT had been minimally raised and stable for the previous 18 months. Clozapine was initiated and titrated to 300mg nocte over two weeks. There were no obvious side-effects but the patient’s mental state had markedly improved. However, five weeks into treatment he began feeling unwell; with anorexia, abdominal pain and vomiting. He attended accident and emergency where blood investigations revealed his ALT had risen to 732U/L. His alkaline phosphatase at 172U/L (normal range 40–130U/L) and gamma-glutamyl transpeptidase of 145U/L (normal range 10–70U/L) were also raised. However, his bilirubin was normal. In addition there was a marked eosinophilia of 2.51x10^9/L (normal range 0.02–0.50x10^9/L).

Symptoms persisted and the patient underwent a range of investigations. An abdominal ultrasound showed that the liver was...
‘diffusely echogenic’ suggestive of an underlying hepatitis. Magnetic resonance cholangiopancreatography reported no evidence of pancreatitis or masses. Hepatitis A, B and C serology tests were negative as was Cytomegalovirus (CMV). However, Epstein-Barr virus (EBV) serology demonstrated evidence of previous infection greater than three months previously. EBV hepatitis tends to present as mild and self-limiting during an acute EBV infection.\(^5\) Caeruloplasmin levels were normal and alpha 1 antitrypsin was just slightly above the upper range. Autoantibody screening was negative for mitochondrial and liver microsome antibodies. Smooth muscle antibodies were detected and are present in 50% of patients with active hepatitis.\(^5\) The patient proceeded to have a liver biopsy which the pathologist reported as showing ‘mild to moderate steatohepatitis’ and ‘quite marked perivenular inflammation’. It concluded that the appearances were ‘more typical of a non-alcoholic steatohepatitis, possibly drug related’.

Clozapine was subsequently stopped and the mainstay of hospital management was supportive. The patient went on to make a full recovery with his LFTs and eosinophils improving rapidly. Within a few weeks they were back to within normal range.

On discharge the patient was still on his risperidone long-acting injection and risperidone 6mg daily. Unfortunately his psychotic symptoms started to worsen with him becoming more withdrawn and his persecutory delusions worsening. After discussion with gastroenterology it was decided to cautiously rechallenge with clozapine. Baseline bloods were normal prior to recommencement. Five days after recommencing clozapine the patient was systemically well with no signs or symptoms of hepatic disease. LFTs were rechecked and his ALT had risen again to 438 U/L with an accompanying eosinophilia. His clozapine was stopped immediately and his ALT and eosinophils once again returned to normal levels (see Figure 1).

Discussion

The above case demonstrates clozapine-induced hepatitis confirmed by rechallenge. This is a rare side-effect although a handful cases have previously been reported, including one that resulted in fatal fulminant hepatic failure.\(^6,10\)

Different mechanisms of drug-induced liver injury have been described. However, the presence of a marked eosinophilia suggests an immunoallergic cause. Further features that support this hypothesis include the early onset of drug injury (within 1–6 weeks) and the rapid rise in ALT on rechallenge.\(^11\) Other classical features of an allergic reaction such as a rash or fever can also be present.\(^12\)

Behavioural and host factors have been associated with this type of liver injury. For example, a lower level of drug-metabolising enzymes is a genetic risk factor.\(^13\) Pertinent in this case is that South Asians have been reported as having lower levels of CYP\(^{12}\).\(^14\) This is the main metabolising enzyme for clozapine. Alcohol and cigarette consumption have also been reported to be triggers.\(^11\) This is important considering the higher prevalence of substance use amongst patients diagnosed with schizophrenia.\(^15\)

Underlying liver conditions can also make an individual more susceptible. Atypical antipsychotic use can increase the risk of metabolic syndrome, which can result in non-alcoholic fatty liver disease.

The exact mechanism of immune-related drug-induced liver injury is unknown but different theories have been put forward. One proposed mechanism is that the drug or its metabolite binds to a liver protein. These drug-protein complexes are then processed by macrophages leading to an adaptive immunity response.\(^12\) Cytotoxic T-cells are then activated which release cytokines resulting in hepatocyte death.\(^16\) The ‘danger hypothesis’ builds on this and postulates that a ‘danger signal’ is required in addition to the drug-protein complex to trigger the above immune response. Damage to intracellular structures within hepatocytes by the drug itself or its reactive metabolites can generate these signals.\(^17,18\) With both proposed mechanisms the innate immune system is triggered. In the liver this consists of Kupffer cells, monocytes and neutrophils, which amplify the inflammatory response.\(^12\)

Additional mechanisms such as mitochondrial injury, endoplasmic reticulum and oxidative stress are also known to play a role.\(^16\)

With clozapine no longer being an option it poses the question of what other strategies are left in treatment-resistant cases. One study has suggested that high-dose olanzapine (greater than BNF limits) may be beneficial.\(^19\) There is some evidence that augmenting antipsychotics with valproate may also be effective, especially when aggression is a feature.\(^20\) Ziprasidone is another augmenting option and is one we actually trialled prior to rechallenge with clozapine as evidence has shown that it may have a positive overall effect on a patient’s mental state.\(^21\) Despite numerous augmenting agents having been trialled there is a lack of high quality evidence to make any specific recommendations.

Conclusion

Although a transient rise in LFTs with clozapine is common, current guidelines suggest monitoring these 4–6
months after starting treatment. This case aims to highlight the importance of clinical vigilance for the rarer side-effect of hepatitis. In particular the 4–5 week period after starting treatment appears to be significant if the underlying mechanism is immunoallergic. Work is ongoing to develop diagnostic biomarkers that can help to identify patients at risk of drug-induced liver injury. Furthermore these patients may merit having their LFTs checked earlier.

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Declaration of interests
No conflicts of interest were declared.

References