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Recurrent Chronic HEV in Severe Combined Immunodeficiency

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To the Editor

Severe combined immunodeficiency (SCID) is a group of genetic disorders characterised by significant impairment of T-cell differentiation, with or without abnormal B and NK cell differentiation. Without haematopoietic stem cell transplant (HSCT), the condition usually leads to an early death, typically as the result of infections. The most frequent genetic cause of SCID affects the common gamma chain, necessary for cytokine signalling. A similar phenotype is observed with mutations in the Janus-associated Kinase 3 (JAK3) gene, the immediate downstream signalling molecule.

Hepatitis E virus (HEV) is a hepatotropic RNA virus that is a rare cause of acute liver failure and does not lead to chronic infections in healthy individuals [1]. It is transferred through the feco-oral route and the course is usually benign and self-limiting in immunocompetent individuals. Acquisition during pregnancy can lead to fulminant liver failure and death [1]. Impaired HEV-specific $CD4^+$ and $CD8^+$ responses to HEV epitopes are associated with the development of chronic hepatitis E [2]. Chronic HEV is a well-described in patients with solid organ transplantation, haematological malignancy and in those receiving systemic chemotherapy [3]. A significant proportion of these patients spontaneously clear HEV on modification of immunosuppression, which is the recommended first line treatment strategy [1].

There are few reports of chronic HEV in primary immunodeficiencies. One case series describes chronic HEV in three individuals with primary immunodeficiency (common variable immune deficiency, idiopathic CD4 lymphopenia, and one undefined primary immunodeficiency), two of whom were treated with ribavirin with one relapse requiring long-term therapy [4].

We describe a 37-year-old Caucasian female with JAK3 SCID and who survived into adulthood without HCST, who then presented with chronic hepatitis E viremia without evidence of chronic liver disease. She has always been resident in the South West of the United Kingdom. She is one of four children from a non-consanguineous marriage of northern European parents. The first male child died at 10 months from *Pneumocystis jirovecii* pneumonia (PJP). The second male (fourth child) had delayed healing of his umbilicus and developed PJP and a variety of infective complications, culminating in death at the age of 9 shortly after HSCT. Genetic analysis both our patient and her younger brother detected compound heterozygous mutations in the JAK3 gene, with residual function leading to more variable clinical phenotype than would be expected [5]. Detailed immunophenotyping has been previously reported [5]. In brief, she had $CD3^+$ T cell lymphopenia primarily with reduced $CD4^+$ T cells and a reduction in $CD4^+$ and $CD8^+$ naïve cells (defined by dual expression of CD62L and CD45RA. T cells had increased markers of activation but had a reduced

proliferative index in response to phytohaemagluttinin. Interestingly there was an increase in TCRgd cells, all of which were Vd2 subset thought to be due to extrathymic peripheral expansion. NK cell numbers were reduced and B cells were increased. Serum total immunoglobulin levels have been persistently normal and therefore intravenous immunoglobulin treatment was not indicated. HSCT was discussed on multiple occasions with the patient and her parents, most recently within the last year, but was declined on each occasion.

Our patient had pneumonia at age 1, severe varicella infection, and occasional ear and urinary tract infections throughout childhood. She was relatively well during her teenage years apart from an intermittently discharging left ear that required a grommet insertion, and recurrent cutaneous warts from age 9 which spontaneously resolved. She has been taking trimethoprim-sulfamethoxazole (TMP-SMX) as antibacterial and *Pneumocystis jirovecii* pneumonia prophylaxis for many years.

During routine follow up at age 31 abnormal liver function was noted (ALT 80 IU/L [normal 10-36 iu/L], ALP 120 U/L [30-130 U/L], bilirubin 4 µmol/L [0-20 µmol/L] and albumin 45 g/L [35-50 g/L]. The only travel history was a caravan holiday on a beach in South West England. Her family was well, and while she worked at an aged care facility there was no report of illness at the facility. Her alcohol intake was negligible. Physical examination was normal with no hepatomegaly or features of chronic liver disease. Viral serology was negative for hepatitis A, B and C and autoimmune liver screen was negative. Liver ultrasound demonstrated fatty infiltration. Serology was positive for HEV IgG and IgM. HEV RNA level was 53000 IU/ml. HEV genotyping is not routinely performed but genotype 3 is most prevalent in the patient's region. She failed to clear the virus spontaneously and was started on oral ribavirin 600mg twice daily for 24 weeks. Pegylated interferon alpha treatment was not considered as there is limited evidence of efficacy [1]. HEV RNA was undetectable in blood within 3 weeks of starting treatment (and remained undetectable throughout her treatment course), and liver function had completely normalised after 1-month of treatment. HEV RNA levels remained undetectable in blood and stool at 1 year follow up.

Two years later elevated ALT was once again noted. HEV RNA level was 1.46 million IU/ml. She was restarted on a planned 48 week course of ribavirin with advice regarding contraception. HEV RNA became undetectable in the blood and stool within two and four weeks respectively and remained undetectable throughout treatment. At week 28 of treatment, she developed lower abdominal pain, heavy vaginal bleeding and passed what may have been a fetus. Ribavirin therapy was discontinued at week 33 when she had a positive urine HCG pregnancy test (despite reinforcement of the strong advice to avoid pregnancy whilst on ribavirin/TMP-SMX). She developed further vaginal bleeding and suffered a spontaneous miscarriage. She was not recommenced on ribavirin and antibiotic prophylaxis was switched to amoxicillin rather than TMP-SMX given her strong desire for pregnancy. She has had negative HEV RNA in blood and stool and normal liver function 52 weeks after completing her last treatment course.

Pregnancy was achieved 12 months later, and during the pregnancy she was found to have extensive Bowen's disease (squamous cell carcinoma *in situ*) on her chest and abdomen, most likely secondary to human papilloma virus infection. This progressed during the antepartum period, likely due to the relative immunosuppression that occurs in late pregnancy. A healthy male baby was delivered successfully via classical caesarean section (to avoid the area affected by Bowen's disease) and

remains well at 12 months of age. She has since had extensive surgical resection of her Bowen's disease, albeit with prolonged healing of the wound.

This case demonstrates that HEV is an important consideration and may be under-recognised in primary immunodeficiencies as it is often asymptomatic [may need ref]. Heightened awareness of HEV is required in areas of high prevalence. HEV IgG and IgM should be assessed as part of the routine investigations of patients with impaired liver function, and in patients with predominantly humoral immunodeficiencies HEV RNA should be included due to the potential failure to seroconvert. Chronic HEV infection is well described in the solid organ transplant population, in whom modification of immunosuppression is sometimes sufficient to enable spontaneous clearance of the infection. Where this fails, evidence suggests a 24 week course of ribavirin will induce remission in the majority. In patients with SCID, there is no evidence based treatment strategy for chronic HEV. However, this case demonstrates that ribavirin can be a successful treatment option with an initial 24 week course. Post treatment, these patients are at risk of hepatitis E reactivation and re-infection, and this should be monitored actively during follow up.

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