SUPPORTING PARENTS TO MANAGE CHRONIC DIABETES MORTALITY TRENDS 1990 TO 2010 IN THE UK COMPARED WITH THE EU15 AND THE USA

Aims We investigated whether the UK has higher child and youth diabetes mortality than in comparable European countries and the USA.

Methods We obtained data from the WHO World Mortality Database for the UK, the USA and the EU15+ (the 15 countries of the EU in 2004 plus Australia, Canada and Norway) for 1990 to 2010. Diabetes mortality rates were calculated for 1–14 and 15–24 year olds. Multilevel longitudinal Poisson regression models were constructed including all country-level data from 1990–2010 (378 country years) comparing the UK with the EU15+ and the USA. Graphics show average mortality across the EU15+.

Results Mortality trends are shown in Figure 1 for 1–14 year olds (both sexes) and Figure 2 (males) and Figure 3 (females) for 15–24 year olds. In 1990 the UK had higher mortality than the EU15+ amongst 1–14yo (p = 0.004) but not amongst 15–24yo (p > 0.2 both sexes). Diabetes mortality did not significantly change in the EU15+ across the study period in any age group. In contrast, amongst 1–14 year olds the UK had a significantly higher rate of decline than the EU15+ (negative slope coefficient, p = 0.03). UK mortality rose amongst 15–24 year olds compared with the EU15+ (positive slope coefficients, p < 0.0001 both sexes). In 1990, the UK had higher diabetes mortality than the US in 1–14 year olds (p < 0.0001) but lower amongst 15–24 year olds (p < 0.0001 both sexes). The USA had little change in diabetes mortality amongst 1–14 year olds but a significant rise in diabetes mortality amongst 15–24 year olds (p < 0.0001 both sexes). The UK had a greater rate of mortality decline that the USA amongst 1–14 year olds (negative slope...
features consist of recurrent episodes of haemolytic anaemia, thrombocytopenia and renal failure with biopsy evidence of thrombotic microangiopathy.

Mutations in complement regulatory genes account for approximately 70% of cases. More recently, components of the coagulation cascade, such as DGKE, have been implicated in the aetiopathogenesis of aHUS. We have identified a novel mutation in protease–activated receptor 2 (PAR2) in a patient with an aHUS phenotype.

Methods Whole Exome Sequencing (WES) was performed on a child presenting at the age of 3 years with nephrotic range proteinuria and biopsy evidence of thrombotic microangiopathy, thrombocytopenia and haemolytic anaemia. One year from presentation, his renal function recovered to baseline but he continues to experience episodic haemolytic anaemia and thrombocytopenia. Of note, there is a familial history of relapsing thrombocytopenia affecting the patient’s father and aunt.

Results WES did not demonstrate any mutations in known aHUS genes. A novel mutations in PAR2 (Y345H) was identified, in silico analysis of this classified this as deleterious. This mutation was not detected in databases of healthy controls.

Sequence analysis demonstrated segregation in affected family members (Figure 1).

Western blot analysis suggests reduced PAR2 expression in the patient’s serum compared to controls. We also show that PAR2 is expressed in glomerular cells (Figures 2 and 3).

Discussion PAR2 is a G-protein coupled receptor, which is activated by a number of pro-inflammatory and coagulation mediators. Activation of this receptor causes a positive feedback loop, leading to a pro-thrombotic state that may result in pathological platelet activation and endothelial dysfunction. As there are high levels of PAR2 in the kidney, this pro-thrombotic state may lead to the thrombotic microangiopathy seen in aHUS.

PAR2 has additional roles in complement regulation that are less well defined. It is known to cause down-regulation of DAF, which is an important regulator of the complement pathway.

Further analysis of genetically undefined cases of TMA and MPGN are required for PAR2 mutational screening to determine