Correspondence

Hepatitis E virus and systemic sclerosis

Sir,

We read with great interest the letter by C.H. Wang and S.Y. Tschen reporting a high prevalence of antibodies against hepatitis E virus (anti-HEV) in different autoimmune disorders, especially primary biliary cirrhosis. This disease can be associated with another fibrosing condition, systemic sclerosis. The pathogenesis of systemic sclerosis (SSc) is related to overproduction of collagen by altered fibroblasts, vascular endothelium damage, serum and cell-mediated immune alterations; these mechanisms can variably contribute to the fibrosis of the skin and internal organs observed in SSc patients. However, the aetiology of SSc remains still unknown; it has been hypothesized that an infectious agent can be the trigger factor of the disease, as for other autoimmune disorders such as systemic lupus erythematosus, Sjögren’s syndrome, Graves’ disease, type 1 diabetes mellitus, etc. On these basis, we evaluated the presence of anti-HEV in the sera of 50 unselected SSc patients (6 males, aged 48.6 ± 11 years, disease duration 8.3 ± 6.0 years, mean ± SD) followed at the Rheumatology Unit of the University of Pisa. Diagnosis of SSc and patients’ clinico-serological assessment were carried out as previously described. Anti-HEV were detected by means of a commercially-available kit (ABBOTT HEV EIA). All sera tested negative for the presence of anti-HEV antibodies. These findings suggest that HEV is not involved in the pathogenesis of SSc. The actual prevalence and the pathogenetic role of HEV in other autoimmune disorders should be confirmed in larger patients’ populations. Other hepatotropic and lymphotropic viruses such as hepatitis C virus and Epstein-Barr virus have been related to various autoimmune and lymphoproliferative disorders. Thus, the possible HEV lymphotropism should be investigated to better evaluate the hypothesis of a pathogenetic role for this virus in some immune-mediated disorders.

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References


Mitochondrial defects and endocrine dysfunction

Sir,

We read with interest the review article on mitochondrial medicine by Chinnery and Turnbull (QJM 1997; 90:657–67). Hypoparathyroidism is referred to as a recently-described endocrinopathy associated with mitochondrial disorders. Both the references cited (34 and 35) were cases of Kearns-Sayre syndrome and we are not aware of any patient with only the 3243 MELAS mutation. We have seen a patient (44y,f) with proven mutation of MELAS syndrome (A. to G. transition the 3243rd nucleotide position of t-RNA (Leu (UUR) gene of mitochondrial DNA) who has NIDDM, bilateral optic atrophy and sensorineural deafness, stroke-like episode, myoclonic seizure, short stature, intestinal pseudo obstruction, lactic acidemia (without acidosis) and primary hypoparathyroidism. She presented with diabetes mellitus and symptomatic hypocalcaemia. Hypoparathyroidism was diagnosed on the basis of a low corrected serum calcium (1.80, normal 2.10 to 2.60 mmol/l), high serum phosphate (1.78, normal 0.80 to 1.70 mmol/l) and low serum PTH (0.4, normal 1.3 to 8.5 pmol/l). She was successfully treated with Calcitriol (0.75 mcg daily) with clinical and biochemical improvement.

Hypoparathyroidism with MELAS syndrome has
been reported at least twice before. In the first case,\(^1\) deletion of mt DNA was identified along with MELAS mutation and in the second,\(^2\) a new additional mutation was identified at a highly-conserved position in the t-RNA molecule close to the MELAS mutation. However, in our case neither a new mutation nor a major deletion of mtDNA was identified. The exact pathogenesis of hypoparathyroidism is not clear but as in other endocrine organ, the parathyroid gland is also dependent on oxidative phosphorylation. We speculate that mtDNA abnormalities reduce ATP production, leading to an impairment of hormone synthesis (or release) or to a decrease in number of cells, although the exact mechanism is not clear.

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References


Sir,

The association of primary hypoparathyroidism and the A to G transition at nucleotide position 3243 of the mitochondrial DNA (mtDNA) L-chain further highlights the genetic and phenotypic diversity of mitochondrial disease. As Bhattacharyya and Tymms illustrate, distinct mtDNA defects such as the A3243G mutation and the ‘common’ deletion may both cause hypoparathyroidism, and yet the same genetic defect may cause a severe encephalomyopathy in one individual, and diabetes with deafness in another. Endocrine gland dysfunction may be the presenting feature of mtDNA disease, either in isolation, or as part of a polyendocrinopathy,\(^1,2\) and physicians who care for patients with mitochondrial disease should maintain a high index of suspicion for an underlying endocrine disorder.

The aetiology of the endocrine abnormalities which accompany mtDNA disease is far from clear. Endocrine organs are heavily dependent upon oxidative phosphorylation, and it is likely that a respiratory chain defect would contribute to endocrine organ dysfunction.\(^3\) However, endocrine organ-specific autoantibodies have been found in patients with mitochondrial disease. For example, diabetes mellitus affects at least 15% of individuals who harbour the A3243G mutation,\(^4\) and in one study, 42% patients with presumed mitochondrial diabetes had significant titres of anti-pancreatic islet cell antibodies.\(^5\) It is uncertain whether the immunological abnormalities are the cause, or the consequence of the organ damage.\(^6\) MtDNA transcripts are expressed on the cell surface, and in mice, mtDNA encodes for a maternally-transmitted HLA antigen.\(^7\) It is possible that a mtDNA mutation leads to the expression of novel cell-surface protein which triggers an autoimmune response.\(^8\) Alternatively, the tissue damage due to the primary mitochondrial dysfunction may result in the presentation of novel auto-antigens.\(^9\) At present we can only speculate, but the patient described by Bhattacharyya and Tymms further adds to the broad phenotype which can be associated with the A3243G mutation, and highlights the importance of endocrine dysfunction in patients with mtDNA disease.

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References


