

Visual disturbances in dengue fever: an answer at last?

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ABSTRACT

Visual disturbances in dengue infection are uncommon but may result in permanent visual impairment. We report a 32-year-old Chinese woman with dengue infection and she developed retinal haemorrhage, retinal vasculitis and macular detachment. Autoimmune screen revealed a low C4 complement level, possibly due to partial C4 complement deficiency. The patient was treated with steroids and there was significant improvement in her vision. Partial C4 deficiency predisposes to autoimmune disease, and patients with pre-existing low C4 levels may be susceptible to ocular complications in dengue infection. Interestingly, previous case reports of ophthalmic complications of dengue infection occurred in young female patients, who are likewise predisposed to autoimmune disease. In conclusion, in individuals predisposed to autoimmune disease (females and patients with partial C4 deficiency), dengue infection may provide the antigenic trigger for immune complex deposition and retinal vasculitis. Steroids may have an important role in the treatment of this condition.

Keywords: C4 complement deficiency, dengue haemorrhagic fever, retinal vasculitis

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INTRODUCTION

Visual disturbances in dengue fever are uncommon but may result in permanent visual impairment. Retinal haemorrhages, microinfarctions and optic neuritis were previously reported in a tourist with dengue fever.⁽¹⁾ There have been several reports of ocular complications of dengue fever in the recent literature.^(2–6) The pathogenesis and treatment options of dengue-related ocular complications are hitherto poorly established. We report our recent experience with a similar case that was investigated to elucidate the possible underlying pathogenesis. Treatment was instituted accordingly and the patient's condition improved.

CASE REPORT

A previously-healthy 32-year-old Chinese woman presented with fever for five days. She then developed a rash over the limbs and trunk, and gum bleeding. She had a generalised erythematous macular rash with islands of sparing and fine petechiae, associated with thrombocytopenia ($65,000/\text{mm}^3$) and neutropenia ($1,760/\text{mm}^3$). This was consistent with a clinical diagnosis of dengue haemorrhagic fever (DHF). The diagnosis was confirmed by a positive dengue IgM. Albumin level

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Fig. 1 Fundal photograph shows haemorrhages at the discs which are mildly swollen, retinal arteriolar sheathing and neurosensory detachment of the macula.

was 43 g/L, prothrombin time 10.2 seconds (normal 10.7–13.4 seconds) and partial thromboplastin time 33.8 seconds (normal 27.8–39.6 seconds). Haematocrit level was 41.5% (normal 36%–46%).

Two days later, she complained of sudden onset of blurred vision. This occurred on Day 7 of onset of fever and coincided with her lowest platelet count of 29,000/mm³. Bilateral best-corrected visual acuity was 6/120. Fundoscopy revealed bilateral mild vitreous haemorrhage, retinal haemorrhage, sheathing of macular arterioles, swollen optic discs and macular detachment (Fig. 1). Fluorescein angiography showed bilateral macular arteriolar leakage and staining of dye. A diagnosis of dengue maculopathy was made. Autoimmune screen was done to elucidate for a possible immune-related pathology. Anti-nuclear antibody, anti-double-stranded DNA, anti-neutrophilic cytoplasmic antibody, anticardiolipin antibody, lupus anticoagulant and rheumatoid factor were all negative. Erythrocyte sedimentation rate was normal. Serum C4 complement level was low (0.18 g/L, normal 0.2–0.72) with normal C3 level. Urinalysis revealed the presence of microalbuminuria (34.0 mg/L). Dengue polymerase chain reaction (PCR), which was done five days after admission, was negative.

In view of the severity of her visual symptoms and findings of vasculitis on angiography, the decision was made to commence on steroid treatment. Intravenous (IV) methylprednisolone (250 mg 6 hourly) was immediately started. After initial improvement, her vision deteriorated after receiving seven doses of IV methylprednisolone over two days. In view of the immune complex deposition, IV immunoglobulin (0.4 g/kg/day) was started and methylprednisolone was discontinued. Three days after the steroids were stopped, the patient was restarted on IV hydrocortisone 100 mg 6 hourly when the serum complement results returned. Six days after steroids were restarted, her vision improved dramatically to 6/15 bilaterally. The microalbuminuria also decreased by 50%. She was maintained on IV hydrocortisone for one week and was subsequently discharged with a tapering dosage of oral prednisolone, starting from 50 mg per day. Outpatient review one week later showed further improvement of vision to 6/12. Repeat serum C4 remained low after clinical recovery from dengue fever (0.13 g/L). Hence, the low C4 levels were unlikely to be due to dengue infection itself. The patient continues to remain well.

DISCUSSION

DHF is defined by the World Health Organisation as dengue fever associated with thrombocytopenia ($< 100 \times 10^9$ cells/L) and haemoconcentration (haematocrit $> 20\%$

above baseline).⁽⁷⁾ Ocular manifestations of DHF are rare, but there have been an increasing number of cases reported in recent literature.^(8–10) The main ocular findings include macular oedema and blot haemorrhages. A majority of patients were reported to have residual visual impairment.⁽¹⁰⁾ The pathogenesis of ocular complications in dengue fever is not fully understood. The most common ocular findings are haemorrhage and macular oedema. Thrombocytopenia in severe dengue may predispose towards haemorrhage. The development of retinal haemorrhage implies that local injury to the retinal vessels has occurred. The cause of this remains unknown in DHF. The vitreous haemorrhage seen in our patient is not commonly reported in DHF. Although rare, bilateral vitreous haemorrhage has been reported in DHF.⁽¹¹⁾ On the other hand, increased vascular permeability in response to immune-mediated cytokine release (capillary leak syndrome) is known to occur in DHF. This may account for the macular oedema seen in our patient, but would not account for the microinfarctions, retinal vasculitis and macular detachment.

We postulate that the vasculitis may be due to immune complex deposition on the walls of the small ocular blood vessels. Dengue viraemia incites antibody production, which if overwhelming, causes deposition of viral antigen-antibody immune complexes resulting in inflammation of the retinal vessels. In addition, the microalbuminuria indicates renal tubular damage by similar immune complex deposition in the kidneys. The dramatic improvement after steroid therapy supports this theory of an underlying immunological process. Direct viral invasion is unlikely as the patient was aviraemic (dengue PCR negative) at that time. An interesting feature in this patient is the isolated low C4 complement level, possibly due to an underlying heterozygous partial C4 complement deficiency. This condition has been known to predispose to systemic lupus erythematosus (SLE) when triggered by increased concentrations of immune complexes.^(12–14) Dengue viraemia may be the trigger for immune complex formation in patients who are predisposed to developing autoimmune disease. A young girl with dengue infection and retinal vasculitis was reported to subsequently develop SLE.⁽¹⁵⁾

It is noteworthy that previous reports of ocular manifestations of dengue infection were predominantly in young female patients.^(4,6,8,9) Thus, in individuals predisposed to autoimmune disease (females and patients with partial C4 deficiency), dengue infection may provide the antigenic trigger for immune complex deposition and subsequent retinal vasculitis. In conclusion, there may be an immunological basis for ocular complications in dengue fever, with young female patients being especially susceptible. Further work is important in this area as steroid treatment may

then be recommended as early treatment to avert a potentially devastating condition.

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