Persistent intraocular rubella infection in a patient with Fuch’s uveitis and congenital rubella syndrome

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Abstract

There is growing evidence for the role of rubella virus in Fuch’s uveitis syndrome (FUS). This report is the first to show persistent intraocular rubella virus in a 28-year-old man with congenital rubella syndrome (CRS), who presented with blurred vision and was diagnosed with FUS.

Case report

A 28 year-old man of Afro-Caribbean descent was referred to a tertiary hospital in 2006 with progressively worsening vision in both eyes. There was no history of pain, conjunctival injection discharge, photophobia, photopsia or floaters. He had been diagnosed at birth with congenital rubella syndrome, following a clinical diagnosis of maternal rubella in pregnancy and presentation with profoundly deafness and cataracts. He did not have any cardiac defects. His visual acuities on presentation in 2006 were 6/36 and 6/12 in the right and left eye respectively. Examination revealed bilateral anterior uveitis with stellate keratic precipitates as well as bilateral posterior subcapsular lens opacities. Intraocular pressures were within normal limits in both eyes. Dilated fundus examination was normal.

The clinical diagnosis of Fuchs uveitis syndrome (FUS) was made based on the presence of a bilateral low-grade anterior uveitis with typical keratic precipitates and the absence of posterior synechiae or acute symptoms of pain, redness and photophobia. Investigations for other causes of uveitis were carried out including serum angiotensinogen converting enzyme, syphilis serology and anti nuclear antibody titers, which were all negative. The full blood count, renal and liver function tests and ESR were normal and the sickle cell screen was negative. The serum rubella IgM was negative and the rubella IgG was positive.
His reduced visual acuity was attributed to his bilateral lens opacities, which is a common feature of FUS. Right followed by left eye phacoemulsification cataract extraction and intraocular lens implantation was performed under general anaesthesia to improve vision. One hundred microlitre samples of aqueous humour were aspirated through a paracentesis prior to both cataract surgeries. The rest of the operations were performed in a standard manner and without complications. The postoperative treatment regime consisted of hourly dexamethasone 0.1% drops that were tapered over 6 weeks and chloramphenicol 0.5% drops qds for 1 week.

A venous blood sample, urine sample and throat swabs were collected for serological and microbiological investigations. The serum sample confirmed serological evidence of past rubella infection with an unusually high titre (Table 1). Samples of aqueous fluid were sent to the national rubella reference laboratory at Colindale for detection of rubella RNA and intra-ocular antibody production, by calculating the rubella specific antibody index (AIrub) based upon the Goldmann-Witmer Index (GW-I)\(^1\). This compares the relative levels of specific antibody in aqueous and serum samples and compares with the relative levels of total IgG (see below).

Total IgG ratio (QigG) = Aqueous Humour total IgG / Serum total IgG

Rubella ratio (Qrub) = Aqueous Humour rubella IgG / Serum rubella IgG

Rubella antibody index (AIrub) = (Qrub) / (QigG)

There was evidence of intraocular antibody synthesis against rubella virus from the right and left eye AH samples (Table 1). An AI>3 is considered consistent with local antibody production. It should be noted that the AIrub from the left eye AH sample was calculated on October 16, 2017.
from the previously obtained serum IgG that could have changed during this time. Antibody for herpes simplex virus and varicella zoster virus were tested as control antibodies, and were within normal limits. There was no evidence of intraocular antibody synthesis for herpes simplex virus or varicella zoster virus as no antibodies towards these viruses were detected. There was no rubella virus RNA detected in serum, plasma, whole blood on EDTA, throat swabs or urine samples by rubella nested reverse transcriptase polymerase chain reaction (RT-PCR). Rubella virus RNA was detected, but at low level (based on the intensity of the band) in both eyes, and confirmed on sequencing of a 252 base pair portion of the rubella virus glycoprotein E1. Although the sequence from both eyes (right eye, GenBank EF210070; left eye, GenBank EU240897) revealed the rubella virus was of the same genotype (1g) the sequences were not identical with 5 differences in the region sequenced. This variation is most likely explained by independent evolution in the left and right eyes, and unlikely to represent sequencing artifact.

The results in this case show evidence of persistent rubella virus in aqueous humour and localised intraocular rubella antibody synthesis in the anterior chamber of a man with a known history of CRS. The profound deafness since birth and presence of rubella IgG support the diagnosis of CRS. In addition, the diagnosis of CRS is in keeping with the rubella epidemic in 1978, when there were approximately 50 CRS births and 800 terminations of pregnancy due to rubella disease in England, Scotland and Wales. Our findings would suggest that congenital rubella infection could be the cause underlying this patient’s bilateral FUS.
This is the first report of FUS in a CRS patient with evidence of intraocular rubella virus antibody synthesis, rubella virus RNA and genotyping of the virus by sequencing. The difference in rubella virus sequence between the eyes is supporting evidence of independent and persistent replication in both eyes since birth. This case adds to the growing body of evidence for the role of rubella virus in the pathogenesis of FUS.

The diagnosis of Fuch’s uveitis syndrome remains clinical and its aetiology is still uncertain. Several recent observations have been published linking rubella virus to FUS; however, the current evidence is still inconclusive. Rubella virus is a single-stranded positive sense RNA virus, the only member of the genus Rubivirus and belongs to the family Togaviridae. The clinical features of rubella are usually an acute exanthematous infection that may be preceded or occur concurrently with fever and lymphadenopathy; it is usually less severe in children than adults. Systemic manifestations can occur but complications including transient thrombocytopenia (1 in 3500) and post-infections encephalopathy (1 in 5000 to 1 in 10000) are not common. The initial report on the teratogenic effects of rubella described the association between congenital cataracts and maternal rubella. Rubella infection in early gestation was subsequently associated with an array of congenital defects including cataracts, congenital glaucoma, congenital heart disease, hearing loss and pigmentary retinopathy. Other clinical manifestations include purpura, splenomegaly, microcephaly, developmental delay, meningo-encephalitis, radiolucent bone disease and jaundice. Rubella virus has been observed to persist with CRS in contrast to acute postnatal infection though the mechanism remains unknown. A distinct cellular response has been suggested as rubella virus was demonstrated to induce apoptosis in differentiated cells.
FUS has been defined as an intraocular syndrome with characteristic signs that include iris heterochromia, low grade anterior uveitis and cataract. It has previously been described that infections with herpes simplex virus, toxoplasmosis and toxocariosis may be associated with ocular disorders with similarity to FUS. In addition to this, a role in the pathogenesis for FUS has been proposed for autoantibodies against cornea, increased intraocular immunoglobulin G (IgG), retinitis pigmentosa and trauma. However, there is growing evidence within the last 6 years for the role of rubella virus as a specific pathogen responsible for FUS and has been proposed to occur due to chronic rubella virus persistence following infection. It has been demonstrated that all (52 of 52) or the majority (13 of 14) of patients with ocular characteristics consistent with FUS had evidence of intraocular antibody production against rubella virus. Furthermore, rubella virus genome was detected by polymerase chain reaction (PCR) in a proportion (5 of 28) of patient’s aqueous humour samples in the 2004 study.

There is further evidence to support the association of rubella virus and FUS due to an observed decrease (4.48% down to 0.62%) in the proportion of patients with FUS in a tertiary ophthalmology centre since the introduction of the US rubella vaccination program that has lead to the virtual elimination of rubella virus. This observation was not seen for patients with idiopathic chronic uveitis or idiopathic chronic granulomatous uveitis.

Moreover, the proportion of foreign-born patients with FUS who were not likely to be vaccinated increased from 24-25% to 42-55% following the vaccination program.
The clinical profile of patients with rubella virus-associated uveitis compared to those with chronic anterior uveitis have been shown to be younger at time of initial ophthalmologic presentation and occur more frequently with unilateral ocular disease, keratic precipitates, iris atrophy and/or heterochromia, associated vitreous opacities and cataract. In particular, a combination of keratic precipitates, absence of posterior synechiae, cataract, and vitreous opacities occurred more often in those with rubella virus. In addition, a case report that is in support of FUS due to postnatal rubella virus infection has shown that rubella virus-associated uveitis may present during childhood; this case also demonstrated the susceptibility of an unvaccinated child to uveitis following rubella virus infection. However, the variety and combinations of clinical features that are observed with FUS make it difficult to conclusively prove a rubella virus-associated uveitis. Furthermore, the pathogenesis of FUS due to rubella virus and whether it is maintained by the virus or for instance, immune-mediated, remains unclear.

FUS has not previously been reported as a manifestation of CRS. Although, cataracts have been observed to occur early in life in 13 patients with CRS in whom glaucoma was diagnosed 3 to 22 years after birth. In addition, keratic precipitates were noted without any other evidence of acute ocular inflammation in 5 of these patients. Ernest Fuchs’ hypothesis was based on an observed heterochromia at birth or early childhood whereas FUS may represent a delayed manifestation of CRS. However, some patients with FUS have been noted to not have heterochromia as infants.

Structural eye defects as a result of CRS are understood to be due to cytopathic effect when maternal infection occurs prior to eight weeks. The evidence to support direct
The cytopathic effect is based upon differing grades of rubella virus-induced apoptosis in cell lines in vitro and could account for the discriminatory organ damage observed in CRS.

The late ocular complications of CRS and some of the characteristic features observed in patients with FUS could be due to persistence of rubella virus. The mechanism for FUS in patients with CRS is not apparent though and the likely incidence unknown. Overall, the pathogenesis of FUS remains uncertain and the role of rubella virus is not fully understood.

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### Table 1 Patient samples for Rubella virus testing

<table>
<thead>
<tr>
<th>Sample</th>
<th>Date</th>
<th>Rubella IgM EIA (Microimmune)</th>
<th>Rubella IgG EIA (Siemens Enzygnost) IU/ml</th>
<th>Rubella virus RNA (nested PCR)</th>
<th>Total IgG mg/l</th>
<th>Total IgG ratio (QIgG)</th>
<th>Rubella IgG ratio (QRub)</th>
<th>Rubella antibody index (AIRub)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>November 2006</td>
<td>Negative</td>
<td>Not detected</td>
<td>Positive: 15823.5</td>
<td>Not detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plasma</td>
<td>November 2006</td>
<td>-</td>
<td>Not detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blood on EDTA</td>
<td>November 2006</td>
<td>-</td>
<td>Not detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Throat swab</td>
<td>November 2006</td>
<td>-</td>
<td>Not detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urine</td>
<td>November 2006</td>
<td>-</td>
<td>Not detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Right eye lens</td>
<td>November 2006</td>
<td>-</td>
<td>Not detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Right eye aqueous humour</td>
<td>November 2006</td>
<td>-</td>
<td>Positive: 1703.6</td>
<td>Detected</td>
<td>Positive: 29.5</td>
<td>2.20 x 10^4</td>
<td>107.66 x 10^3</td>
<td>48.94</td>
</tr>
<tr>
<td>Left eye lens</td>
<td>March 2007</td>
<td>-</td>
<td>Not detected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Left eye aqueous humour</td>
<td>March 2007</td>
<td>-</td>
<td>Positive: 1212.8</td>
<td>Detected</td>
<td>Positive: 78</td>
<td>5.83 x 10^2</td>
<td>76.65 x 10^3</td>
<td>13.15</td>
</tr>
</tbody>
</table>
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Potential conflicts of interest

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