

## RIFT VALLEY FEVER RETINOPATHY: OBSERVATIONS IN A NEW OUTBREAK

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Rift Valley fever (RVF) is an arthropod-borne viral disease of domestic livestock, particularly sheep and cattle, and humans living in sub-Saharan Africa.<sup>1</sup> The virus was originally isolated in the Rift Valley in Kenya in 1930 during an epizootic of fatal hepatic necrosis and abortion in sheep.<sup>2</sup> Numerous arthropod vectors have been incriminated. Rift Valley fever virus has been isolated from 23 species in five genera of mosquitos.<sup>1</sup> Transmission of RVF virus is also known to occur via aerosols or contact with infected animal blood and tissues.<sup>1</sup>

Before 1975, when four human RVF fatalities and one case of retinitis were reported in South Africa,<sup>3</sup> the disease was only known to cause mild illness in humans.<sup>4-6</sup> In 1977, the virus spread north of the sub-Saharan region, when a major RVF epizootic occurred in the Nile River delta and valley of Egypt.<sup>7</sup> Many of those infected in that outbreak had severe disease with hemorrhagic manifestations or meningoencephalitis.<sup>8,9</sup> Nearly 600 fatalities were reported.<sup>7</sup>

Ocular complications are estimated to occur in approximately 1% of all RVF infections (Arthur RR, unpublished data). Earlier reports of eye involvement present a spectrum of disease ranging from a blurred vision syndrome<sup>10</sup> to macular exudate-like lesions,<sup>11</sup> retinal detachment<sup>12</sup> and retinitis.<sup>13</sup> Cohen and Luntz were the first to report the use of fluorescein angiography to study retinal changes in RVF.<sup>14</sup> Their data suggested that lesions were the result of primary occlusion of the retinal circulation. Siam et al.<sup>15,16</sup> reported detailed photographic and fluorographic descriptions of seven serologically diagnosed cases of RVF retinopathy during the 1977 epidemic in Egypt. These authors suggested vasculitis, retinitis, and vascular occlusion as the primary underlying pathologic changes. During the same epidemic, Ayoub et

al.<sup>17</sup> reported 16 cases showing maculopathy, vascular narrowing and sheathing, and retinal hemorrhages, and argued that the pathology was of an inflammatory rather than an ischemic nature. Although RVF infections have not occurred outside of Africa, RVF retinitis has been reported in travellers returning from Africa to North America<sup>18</sup> and Europe,<sup>19</sup> indicating the pathognomonic nature of the retinal lesions.

Slightly more than one decade later we are reporting a new outbreak of RVF retinopathy occurring in Egypt. During the late summer and early fall of 1993, patients from an area east of the Nile River delta, 120 km northeast of Cairo, sought medical care for visual impairment. All had ocular lesions highly suggestive of RVF retinopathy. RVF first reappeared in Egypt in May 1993 in Aswan Governorate, approximately 800 km south of Cairo, where patients with ocular lesions were positive for anti-RVFFV IgM antibodies<sup>20</sup> (Sobhy MI, presentation at the 1994 Annual Meeting of the Ophthalmological Society of Egypt, Cairo, March 1994).

### Methods

#### *Study Subjects*

Beginning in August 1993 through October 1993, 22 patients were referred to us with symptoms and signs suggestive of RVF. All patients were residents in a narrow agricultural area (El Qassassin, Ismailia Governorate) extending east into the desert from the Nile River delta. During the initial examination of each patient, a detailed history was obtained. These data included the occupation, area of residence, date of onset of fever and visual complaints, as well as other symptoms.

#### *Ophthalmological Procedures*

Anterior segment examinations were performed with a slit lamp. Indirect ophthalmoscopy and slit lamp biomicroscopy were used to examine the fundus. Colored fundus photography and fundus fluorescein angiography (FFA) were done for patients whose media were clear enough to allow good visualization of the retina (12 patients). These procedures were repeated during the period of six to nine months after the initial examination.

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TABLE 1. Fundus signs in 39 affected eyes of 22 suspected RVF patients who were examined during acute and convalescent phases of illness.

	Number of eyes (%)
Initial examinations	
Macular lesion	39 (100)
Paramacular lesion	29 (74)
Vitreous flare	13 (33)
Discoid lesions	10 (26)
Arteriolar narrowing and/or sheathing	9 (23)
Peripheral lesions	2 (5)
Follow-up examinations (six to nine months later)	
Retinal microangiopathies	39 (100)
Macular scars	34 (87)
Optic atrophy	8 (20)
Anterior uveitis	0 (0)

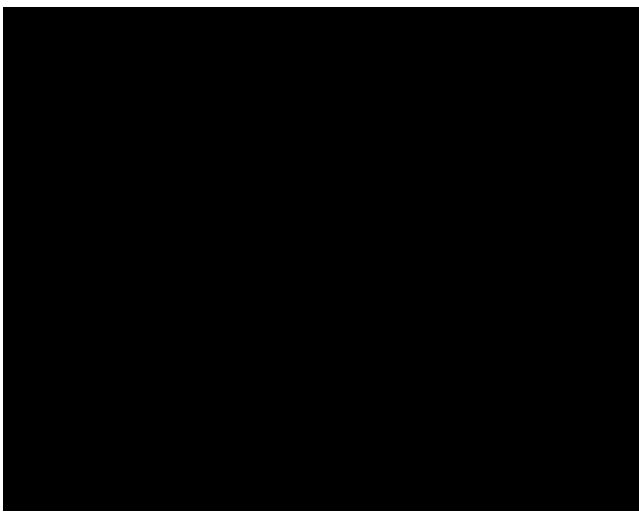


FIGURE 1. A scatter-gram comparing initial visual acuities to those after six to nine months. All acuities either slightly improved or remained unchanged, none deteriorated; NoPL=no perception of light; PL=perception of light; HM=hand movement; CF=counting fingers.

### Viral Serology

Human sera were tested for anti-RVF virus IgM as described by Niklasson and co-workers.<sup>21</sup> Human sera were tested at a dilution of 1:100 by IgM capture ELISA using supernatant RVF virus antigen produced in Vero cells and anti-RVF virus hyperimmune mouse ascitic fluid as the detector antibody. Serum samples were collected two to three weeks after the onset of fever (approximately 10-14 days after the initial examination).

### Results

Serum specimens were collected from only six of the 22 patients because of cultural difficulties associated with performing venipuncture, particularly on female patients. All six patients were positive for anti-RVF virus IgM antibodies, indicating that they had recent infections. Although serological confirmation of recent RVF virus

infections was not feasible in the other 16 patients, all of the patients lived in the same area, presented during a short period when virus transmission was occurring and had lesions with similar appearances. On this basis, they are included in this series of RVF retinopathy cases.

All male patients were farmers and all female patients were housewives. None of the patients were butchers or veterinary workers. Their ages ranged from 34-64 years (mean  $\pm$  SD, 50.3  $\pm$  9.0). There were no patients in the pediatric age group. Fourteen patients were female (63.6%) and eight were male (36.4%). Three patients gave history of contact with aborted animal tissues. This suggests that the mode by which the majority of the patients were infected was via mosquitoes. Fever that lasted from two to seven days, the degree of which could not be precisely determined, was reported by a majority of the patients (81.8%). Periocular pain was reported by 10 patients (45.5%) and only occurred during fever. Headache, a non-specific symptom, was infrequent.

The onset of visual complaints was four to ten days after the onset of fever (mean  $\pm$  SD, 6.4  $\pm$  1.8). Patients reported either blurriness or loss of their vision. Visual acuities ranged from PL to 6/36. All patients either remained of the same visual acuity or showed slight improvement during the period of convalescence (Figure 1). Fundus lesions were seen in both eyes of 17 patients (77.2%) and in only one eye in the other five patients. Fundus examination revealed ill-defined creamy white areas that were macular, paramacular or both, and were all accompanied by macular edema (Figures 2A and B). These lesions occurred outside the arcades in only two patients (9.1%). During the convalescent period, lesions showed resorption of edema fluid, diminished in size, and were replaced at their periphery by retinal microangiopathies (Figures 2C and D). Lesions varied considerably in shape from discoid to semi-discoid or ovoid (Figure 2B) and sometimes had multiple satellite lesions of the same or of a refractile nature (Figure 2A). Intra-lesion hemorrhages were observed in the eyes of several patients. Other lesions included segmental arteriolar narrowing, and hazy media due to vitreous flare.

All the patients in this series received empirical corticosteroid treatment. The dosage was one to two mg/kg/day for one month and was gradually withdrawn. Lesions seen at the time of follow-up reexamination were retinal microangiopathies (Figures 2C and D), macular scars (Figure 2C), and total arteriolar sheathing and optic atrophy. None of the patients showed manifestations of either recent or old anterior uveitis. The incidence of the main fundus signs are summarized in Table 1.

FFA showed areas of early blocking of choroidal fluorescence and later retinal capillary dropout (Figure 3). These changes are suggestive of retinitis etiology. In addition, staining of the walls of the blood vessels in the



FIGURE 2. A composite photograph of both fundi at the initial examination after the onset of visual complaints (a, b) and six months afterwards (c, d). Note the diminution in size of the lesion due to resorption of the surrounding retinal edema, appearance of microangiopathies, and macular scarring (d). At the time of initial examination, anti-RVF virus IgM was present in serum from this patient.

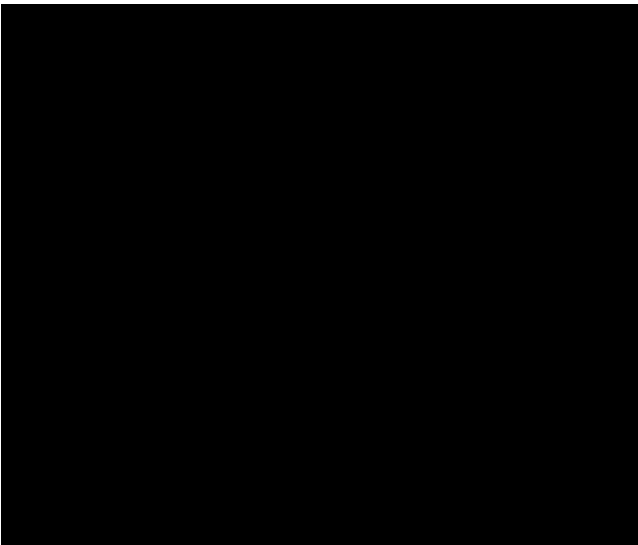


FIGURE 3. FFA of the right eye of the patient in Figure 2 showing macular capillary dropout, and leaking microangiopathies.

macular lesions was noted and was suggestive of associated retinal vasculitis. Retinal ischemia changes probably occurred secondary to macular occlusion caused by vasculitis.

### Discussion

To the best of our knowledge the present series of RVF retinopathy is the largest reported and therefore represents the most complete description of retinal findings. In contrast to a previously published series of the last

epidemic that occurred in Egypt in 1977,<sup>15</sup> none of the patients in the present series showed signs or symptoms of anterior uveitis. Vitreous haze was encountered in a comparable percentage of patients (33.3% versus 28.6% in the previous series). This could be due to either posterior uveitis that occurred during the period of viremia or leakage from inflamed vessels. Another possible explanation is that the early institution of steroid therapy in our patients aborted the development of anterior uveitis and probably aided in the absorption of macular edema, but further assessment of this treatment is needed. As a rule, vitreous haze cleared without residua within a period of a few weeks. In our series, the frequency of involvement of both eyes was comparable to that observed in the previous epidemic in Egypt.<sup>15</sup>

The lack of histopathological material to date has made the pathology of ocular affliction in RVF an issue of speculation based on clinical and fluorographic findings. In a report of brain autopsy performed in a fatal case of RVF,<sup>22</sup> perivascular cuffing and round-cell infiltration were noted. This, together with other previous clinical reports,<sup>15-17</sup> favors an inflammatory nature of the lesion. In this clinical study our findings suggest that the primary pathology is retinitis and retinal vasculitis resulting in vascular arteriolar occlusion. The presence of capillary drop-out areas, later formation of microangiopathies (mostly microaneurysms) and subsequent macular scarring in the areas of the primary lesions indicates secondary microvascular occlusion to infectious retinal vasculitis. The ambiguous term "exudate-like lesions" used by previous investigators<sup>11,12,15-17</sup> is confusing and does not imply a definite pathology; instead, the lesions should be described as "infectious retinitis."

Of additional interest is the question of whether retinal lesions occur in what appear to be uncomplicated RVF infections. Obviously, only individuals with macular or paramacular lesions with impaired vision seek ophthalmological care and are examined. Our findings indicate that RVF retinopathy is more prevalent in females and does not occur in children, phenomena to which at present we have no explanation. Further studies are needed to explore in more detail what factors, in addition to age, predispose the infected subject to develop ocular disease.

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