CASE REPORT

Ocular manifestations of rickettsia in children: common but frequently overlooked

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SUMMARY

We review two cases of ocular manifestations of *Rickettsia conorii* infection in children. A girl who presented unilateral visual loss with focal retinitis and macular oedema and a boy with unilateral central scotoma and bilateral anterior uveitis. Progressive functional and anatomic recovery was observed after oral antibiotics and steroids were initiated.

BACKGROUND

Rickettsial zoonoses are emergent and resurgent acute systemic diseases caused by obligate intracellular gram-negative bacteria. Mediterranean spotted fever (MSF) is endemic in Mediterranean countries, caused by *Rickettsia conorii* and transmitted to humans by contaminated tick's bites (*Rhipicephalus sanguineus*). The microorganisms generally attack endothelial cells leading to vascular injury and tissue necrosis.¹ Systemically, it is characterised by high fever, headache and skin rash. In Portugal, the reported incidence of MSF between 2000 and 2010 was 3.72 cases/10⁵ inhabitants/year.²

Common ocular findings include retinitis, retinal vasculitis and optic disc changes but these are frequently silent.^{3–5} Careful ophthalmological examination with serological evaluation is necessary to promptly initiate treatment and avoid

severe complications such as permanent visual impairment especially in children.

CASE PRESENTATION

Case 1

A 10-year-old girl with no known ophthalmological disorders complained of left eye (LE) acute visual loss. Parents and clinical records reported history of fever associated with a preauricular skin lesion and cervical adenopathy 1 month before with no reference of antibiotic treatment at that time. Parents denied having any pet animals. National vaccination plan was updated. Initial ophthalmological examination revealed LE corrected distance visual acuity (CDVA) of 20/40 and a juxtavascular retinal infiltrate with apparent macular oedema (figure 1A); vitritis was absent. Biomicroscopy, intraocular pressure and right eye (RE) examination were normal.

Case 2

A previously healthy 10-year-old boy presented bilateral progressive visual loss for 2 months, followed by a sudden RE central scotoma. His mother mentioned a recent episode of isolated facial rash without fever that she had associated with solar exposure. The family reported having a cat pet. The child's national vaccination plan was updated. On initial examination, no cutaneous lesions were detected. Ophthalmological evaluation revealed a CDVA of count fingers at 2 m (≈6.5 feet) and 20/25 for the RE and LE, respectively. Slit-lamp examination showed bilateral anterior chamber cells (2+) with no evident posterior synechiae. Funduscopy revealed bilateral disc oedema, a nasal macular star and a central serous retinal detachment (RD) associated with a choroidal lesion on the right and peripheral bear-track lesions on the left (figure 2A, B); the vitreous was clear bilaterally.

INVESTIGATIONS

Case 1

Left eye spectral domain optical coherence tomography (SD-OCT) demonstrated macular neurosensory RD (figure 1B), and fluorescein angiogram (FA) showed late-frame leakage in the macular area. Blood tests with complete blood cell count, comprehensive metabolic panel, C-reactive protein, erythrocyte sedimentation rate, liver transaminases and serologies for frequent infectious agents (*Toxoplasma gondii*, *Bartonella*, *Borrelia burgdorferi*, *Toxocara*,

Figure 1 Baseline: left eye colour fundus photograph (A) with temporal focus of retinitis and vascular attenuation and spectral domain optical coherence tomography (SD-OCT). (B) Macular oedema with central neurosensory retinal detachment. Third month: no evidence of retinitis or macular oedema on left eye colour fundus photograph (C) and normalised SD-OCT (D).

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Figure 2 Baseline: right eye (A) colour fundus photograph demonstrating disc oedema and nasal macular star (blue arrow); left eye (B) colour fundus photograph evidencing disc oedema and peripheral bear-track lesions (yellow arrows).

Rubella, *R. conorii*, Epstein Barr virus, syphilis, cytomegalovirus, Quantiferon TB gold, HIV, hepatitis B and C virus) were performed. Serology for *R. conorii* was positive—immunoglobulin (Ig)G 128+ and IgM titre 32+, determined by serum immunofluorescence, reference values used in Ricardo Jorge Institute, Porto, Portugal.

Case 2

Right eye FA showed late-frames' leakage (figure 3A) in the area of macular neurosensory RD present on SD-OCT as an inward bulging of the choroid (figure 3B). No cystoid macular oedema or neurosensory RD was present on LE. The patient was submitted to the same blood tests performed in case 1, testing positive for *R. conorii*—IgG titre 64+ and IgM titre 32+, using the same reference values. All other blood tests were within normal range.

TREATMENT

Case 1

The case was discussed with paediatrics department and empirical treatment with trimethoprim/sulfamethoxazole 200 mg/5 mL + 40 mg/5 mL (weight adjusted dosage) and oral deflazacort 25 mg/day was initiated. Favourable clinical and symptoms evolution was noted. Serologies' results were available 2 weeks later and at that time steroid therapy was tapered and trimethoprim/sulfamethoxazole association maintained for a total of 6 weeks.

Case 2

Empiric treatment with oral erythromycin 500 mg twice a day in association with dexamethasone sodium phosphate eye-drops three times a day was started. Since clinical improvement was noted, the treatment was maintained for 3 weeks. At this point, oral deflazacort 20 mg/day with a 5 mg/week reduction plan was introduced and erythromycin was reduced to 250 mg twice a day. Oral treatment was maintained for 2 months and dexamethasone sodium phosphate eye-drops were used for a total of 3 months.

OUTCOME AND FOLLOW-UP

Case 1

Two weeks after initiating treatment, LE CDVA had improved to 20/32, there was no anterior chamber inflammation or vitritis and macular oedema had reduced. At the third month follow-up visit, the patient presented bilateral 20/20 CDVA, no signs of anterior or posterior segment inflammation and no macular oedema (figure 1C, D). On the last follow-up visit, 18 months after treatment completion, the patient remains stable, with no signs of inflammation.

Figure 3 Baseline: right eye fluorescein angiogram (A) showing dye pooling in the macula and spectral domain optical coherence tomography (SD-OCT) (B) evidencing inward choroid bulging with central serous retinal detachment. Three months after recurrence: right eye SD-OCT scan showing discrete external retinal layers' irregularity (C).

Case 2

Three weeks after starting treatment, CDVA had improved to 20/32 and 20/20 on the RE and LE, respectively. Slit-lamp examination revealed bilateral endothelial dust with no anterior chamber cells and discrete disc borders' obscuration was apparent on funduscopy. SD-OCT confirmed a marked decrease in central and temporal neurosensory RD, with choroidal bulging disappearance, but it showed a small perifoveal external retina irregularity. On the second month follow-up visit, ophthalmological examination was normal, with no signs of inflammation, and CDVA was 20/22 and 20/20 for the RE and LE, respectively. SD-OCT examination was unaltered.

At the third month, the patient complained of bilateral eye redness and had self-medicated with topical dexamethasone six times a day for a week. CDVA was now 20/25 and 20/20 on the RE and LE, respectively. The examination revealed bilateral relapse of anterior chamber inflammation and disc oedema.

Blood tests were repeated and *R. conorii* titres remained positive. The case was discussed with the infectious disease department and the patient started on doxycycline 100mg twice a day, deflazacort 10mg/day and topical dexamethasone three times a day. Two weeks later bilateral CDVA was 20/20 and no anterior chamber inflammation was seen, but minor disc oedema persisted. Ultrasonography B-scan was performed with optic disc drusen exclusion. Doxycycline was then stopped and steroids progressively tapered.

Six weeks later, despite no other complaints, bilateral red eye recurred, mild anterior chamber inflammation was noted and CDVA had decreased to 20/22 bilaterally. Oral and topical steroids were reintroduced and complementary study with autoimmunity tests ordered. The autoimmunity panel (human leucocyte antigen (HLA)-B5, HLA-B27, antinuclear antibodies, extractable nuclear antigen screen, anti-DNA ab, anti-dsDNA ab, anti-MPO ab, anti-PR3 ab, rheumatoid factor, C3, C4 and lupus anticoagulant) was negative and steroid treatment progressively reduced.

Three months after the last recurrence, the patient presented 20/20 CDVA bilaterally and no signs of inflammation. SD-OCT maintained small perifoveal external retina irregularities on the RE (figure 3C), and no alterations were evident on the LE.

DISCUSSION

In MSF disease, posterior segment involvement is common but frequently asymptomatic. Clinicians' greatest challenge is to diagnose these infections early in their clinical course, when antibiotic therapy is most effective. In order to accomplish this, a careful dilated fundusoscopic examination, complemented with FA in selected cases, is recommended. In endemic areas, if the triad posterior segment changes, fever and skin rash are present, suspicion of *R. conorii* infection should be high.

Complete blood count and serological panel should be performed to exclude other systemic infections, such as toxoplasmosis, rubella, syphilis, cat scratch disease, toxocara and viral diseases, and antibiotic treatment should be promptly initiated. Doxycycline 100mg/day for 10–14 days is the treatment of choice in adults and children of any age⁶; macrolides are an alternative in pregnant women. Systemic steroids should be associated if severe retinitis threatens the macula, or vitritis, retinal vascular occlusion and optic nerve involvement occur.⁷

In our experience, the girl (case 1) had history of fever and preauricular skin lesion with unilateral acute visual loss 1 month later. The boy (case 2) presented a cutaneous rash without fever and bilateral progressive and severe visual loss for 2 months with sudden RE central scotoma. Both cases appeared in spring/summer season (April and July). Posterior segment alterations found were perivascular focal retinitis and macular oedema in case 1 and bilateral disc oedema, central serous RD with choroid bulging with no vitritis in case 2. Anterior segment was mildly involved in case 2. Our data is in accordance with Khairallah *et al*'s³ who studied 30 patients with serologically proven acute MSF; 25 of whom were asymptomatic. The majority (>80%) had chorioretinal involvement, and inner retinitis was present in at least 30%, typically adjacent to retinal vessels, variable in number, size and retinal layer location. These lesions may occur either by intraretinal rickettsial multiplication or immune complexes and inflammatory cells' deposition in retinal vessels.^{8,9} To diagnose *R. conorii*, serum microimmunofluorescence is widely accepted¹⁰ and considered positive usually with titres of IgM ≥ 64 and IgG ≥ 128 .¹¹ These cut-off values are slightly different from

ours, since reference titres' values used in the Ricardo Jorge Institute are IgG ≥ 128 and/or IgM ≥ 32 . After diagnosis confirmation, previous antibiotic treatment must be adjusted. In case 1, the apparent isolated unilateral focus of (chorio) retinitis raised the suspicion of toxoplasma infection, so the chosen empiric treatment was trimethoprim/sulfamethoxazole associated with deflazacort. Despite the current literature suggesting that *Rickettsia* spp are not responsive to trimethoprim/sulfamethoxazole,¹² our patient's good visual outcome is attributable to the effects of steroids on immune-mediated retinal responses. This was also reported by Kawali *et al*,¹³ who presented several cases of rickettsial retinitis that responded well to treatment with steroids only. In case 2, a macrolide (erythromycin) was chosen as first treatment. There are few reports and no established guidelines for treatment of ocular rickettsioses in children. A Spanish series¹⁴ of seven patients diagnosed with uveitis due to *R. conorii* infection, included an 8-year-old boy with RE posterior uveitis and LE panuveitis that responded well to a course of oral doxycycline. In a series of 30 cases of scrub typhus¹⁵ (caused by *Orientia tsutsugamushi* in the Rickettsiaceae family) in Thai children, there was one 11-year-old boy with documented retinal vasculitis. In this series, 29 children were treated with oral doxycycline and one with oral chloramphenicol, all with good response. None of the series reported steroids use. Both our patients showed functional and anatomic recovery within 2 weeks and the treatment was maintained for 6 weeks. However, recurrence occurred in case 2 and, after excluding autoimmune disorders, doxycycline was introduced despite its possible side effects. In both cases, oral deflazacort was associated. After an 18 and 6 months follow-up period for cases 1 and 2, respectively, both patients showed no signs of anterior or posterior segment inflammation.

In conclusion, a big clinical suspicion is necessary to timely diagnose and treat rickettsial uveitis in children. In these patients, ophthalmological screening is essential to exclude silent but possibly irreversible ocular lesions. Treatment with oral doxycycline should be started as soon as the serological results are known and systemic steroids associated if posterior segment involvement threatens the macula.

Learning points

- ▶ Rickettsial infections are important, emerging infectious causes of uveitis that should be considered in the differential diagnosis of posterior segment inflammation, not only in adults but also in children living in or travelling back from specific endemic areas.
- ▶ Ocular involvement is common in patients with rickettsioses, but frequently asymptomatic and self-limited.
- ▶ Careful dilated ocular examination, complemented by fluorescein angiogram and optical coherence tomography should be performed as well as complete serological evaluation with *Rickettsia conorii* serum immunofluorescence.
- ▶ Empiric antibiotic therapy with doxycycline or a macrolide must be promptly initiated to avoid complications and visual impairment.
- ▶ Very few cases of paediatric ocular Mediterranean spotted fever are described; all of them were treated empirically which poses difficulty in establishing treatment and follow-up guidelines.

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