Ocular inflammatory manifestations induced by dengue virus infection

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Abstract

Dengue infection can produce a wide clinical spectrum of inflammatory manifestations in the eye. Ocular manifestations during the critical period of the disease are more frequently associated with vascular damage induced by the viral protein NS1. Sight-threatening retinal conditions in that period include posterior uveitis and dengue maculopathy. Retinal hemorrhages, edema, vasculitis and exudative retinal detachment are the most frequent presentations of posterior uveitis. SD-OCT and OCTA are tools capable to locate the affected retinal layers and capillary plexus involved in the retinopathy. Although infrequent, neuroophthalmological manifestations are an important cause of visual disturbance, inducing ophthalmological inter-consults in hospitalized patients. Available treatments include supportive measures, systemic corticosteroids and intravenous immunoglobulin. There is an urgent need for clinical studies to test drugs known to restore vascular permeability as well as new antiviral drug candidates.
Keywords: dengue, ocular manifestations, 2020 epidemic.

Manifestaciones inflamatorias oculares inducidas por el virus del dengue

Resumen

La infección por dengue produce un amplio espectro de manifestaciones inflamatorias oculares. Las

que ocurren durante el período crítico de la enfermedad están asociadas con daño vascular inducido por la proteína viral NS1. Las manifestaciones retinales que pone en riesgo la visión del paciente durante este período son las uveítis posteriores y la maculopatía por dengue. Hemorragias, edema y vasculitis retinal junto con el desprendimiento exudativo de retina son las manifestaciones oculares más frecuentes de la uveítis posterior. La tomografía de coherencia óptica de dominio espectral (SD-OCT) y la angiografía tomográfica de coherencia óptica (OCTA) son herramientas útiles, capaces de localizar los plexos capilares afectados en esta retinopatía infecciosa. Aunque infrecuentes (respecto del total de pacientes infectados) las manifestaciones neurooftalmológicas son causa de consulta oftalmológica por síntomas visuales e interconsultas de pacientes hospitalizados. Los tratamientos disponibles incluyen medidas de soporte y asistencia general, corticoides sistémicos y tratamiento con inmunoglobulina intravenosa. Existe una urgente necesidad de ensayos clínicos orientados a testear drogas con conocida actividad estabilizadora de la permeabilidad vascular retinal así también como de drogas antivirales.
Palabras clave: dengue, infecciones oculares.

Manifestações inflamatórias oculares induzidas pelo vírus do dengue

Resumo

A infeção por dengue produz um amplo espectro de manifestações inflamatórias oculares. As que acontecem durante o período crítico da doença estão associadas com dano vascular induzido pela proteína viral NS1. As manifestações retinianas que põem em risco a visão do paciente durante esse período são as uveítes posteriores e a maculopatia por dengue. Hemorragias, edema e vasculite retiniana junto com o desprendimento exudativo de retina são as manifestações oculares mais frequentes da uveíte posterior. A tomografia de coerência óptica de domínio espectral (SD-OCT) e a angiografia tomográfica de coerência óptica (OCTA) são ferramentas úteis, capazes de localizar os plexos capilares afetados nesta retinopatia infeciosa. Embora infrequentes (em relação ao total de pacientes infetados) as manifestações neurooftalmológicas são causa de consulta oftalmológica por sintomas visuais e interconsultas de pacientes hospitalizados. Os tratamentos disponíveis incluem medidas de suporte e assistência geral, corticoides sistêmicos e tratamento com imunoglobulina intravenosa. Existe uma urgente necessidade de ensaios clínicos orientados a testar drogas com conhecida atividade estabilizadora da permeabilidade vascular retiniana como também de drogas antivirais.
Palavras chave: dengue, infeções oculares.

Introduction

Dengue virus (DENV) belongs to the *Flaviviridae* virus family. It is an arbovirus, an arthropod borne virus[1], meaning that the virus is transmitted by an arthropod.

The mosquito *Aedes aegypti* is its main vector in urban settings and *Aedes albopictus* in rural and rainforest areas. The recent expansion of *Aedes aegypti* distribution in the world resulted in a 30 fold increase in the incidence of dengue disease in the last decades[2-3].

DENVs are a group of positive mono-catenary RNA viruses that are antigenically related and grouped according to the human serum response (serotype) in DENV-1 to DENV-4. The genome is an 11 Kb RNA strand with 10 genes coding 3 structural proteins and 7 nonstructural proteins. Protein M and Protein E are the main proteins of the envelope. Protein C forms the capsid. The nonstructural proteins are NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5[1].

Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas. The global incidence of dengue has grown dramatically in recent decades. There are 100-400 million of estimated infections each year. The largest number of dengue cases ever reported globally was in 2019. The American region alone reported 3.1 million cases, with more than 25,000 classified as severe[2]. According to the National Health Ministry, Argentina has more than 92.229 dengue suspected cases since week 31 of 2019 (end of July 2019)[4]. Of those patients, 56492 are confirmed dengue cases. The propaga-

tion of the disease from the north of the country during the first trimester of 2020, resulted in the worst known epidemy of dengue in Argentina. Current prevalent serotypes in Argentina are DENV-1 in the northwest, DENV1- and DENV-4 in the center and DENV-1, DEN-2 and DENV-4 in the northeast of the country. The three serotypes (DENV-1, DENV-2 and DENV-4) were also detected in Buenos Aires province[4].

Each serotype comprises several genotypes that have specific geographical distributions[5]. Five genotypes for DENV-1, 6 for DEN-2, 5 for DENV-3 and 4 genotypes for DNV-4. Infection by any of the serotypes generates a humoral immune response. Antibodies providing protection against all serotypes are called heterotypic antibodies and their protection lasts approximately 3 months. Specific antibodies against the infective serotype (homotypic antibodies) provide homotypic protection which was believed to be lifelong[6]. However, in a recent review of samples from patients in Nicaragua (obtained between epidemic outbreaks 2005 to 2012) homotypic reinfections were found within the same serotype for DENV-1, DENV-2 and DENV-3 serotypes[7]. Analysis of samples from patients reinfected in a large outbreak in Peru 2010-2011 also showed homotypic reinfection of patients with a DENV-2 American-Asian genotype different from the infecting DENV-2 Asian genotype that primarily infected the patients in 1995[8]. Together the data destroyed the dogma: one-time infection by a homologous DENV serotype.

Pathophysiology

The DENV NS1 protein is a complex multifunction protein involved in capsid assembly, host immune system evasion and vascular leakage. DENV NS1 has been shown to circulate as a soluble protein at high levels (1-2 μg/ml), correlating with DENV viremia[9].

The hallmark of severe dengue is increased vascular permeability. Collapse of the vascular lumen as well as increase endothelial markers were shown in small vessels while no signs of endothelial cell (EC) necrosis or EC DENV infection accompanied the above mentioned changes[10]. Vessel hyperpermeability was suggested to be either a direct effect of DENV NS1 on the glycocalyx[11] or a consequence of the function of several cytokines released by PBMC[12] after the activation of Toll-like-receptor-4 TLR4[13]. It was shown that DENV-NS1 can activate sialidases, cathepsin L and heparinases thus triggering the degradation of sialic acid and heparan sulfate at the glycocalyx[14]. DENV NS1 was shown to induce hyperpermeability in all tested human endothelial cells, with maximal effect on pulmonary endothelial cells[15]. The vascular leakage is apparently mediated by the specific interaction and subsequent internalization of NS1 in endothelial cells. Recently, the decrease of EC barrier integrity was associated with the activation of the p38MAPK pathway and it could be restored after the treatment with a p38MAPK inhibitor[16].

Humoral immune response

Antibodies typically protect humans from viruses in 3 ways: A) neutralization (antibody blocks virus interaction with host cell), B) opsonization (antibody coats virus and typically targets it for uptake by macrophages and neutrophils), C) antibody-dependent cellular cytotoxicity (ADCC, where the antibody mediates the destruction of infected cells).

In severe dengue, antibodies play a different detrimental function for the host. Severe dengue most commonly occurs among patients with secondary DENV infections and infants with primary infections. The most widely cited hypothesis for the pathogenesis of severe dengue in a second infection setting is called antibody-dependent enhancement (ADE)[17]. Human serological studies, as well as animal and in vitro models support the ADE hypothesis. Although the exact mechanisms are not clear, ADE is the process in which DENV complexed with non-neutralizing antibodies can enter into a greater proportion of cells of the mononuclear lineage, such as monocytes, macrophages and dendritic cells, thus increasing the quantity of infected cells and consequently increasing virus production. In

dengue, non-neutralizing heterotypic IgG anti-DENV antibodies produced during first DENV infection can form antibody-DENV complexes in the second infection that can allow uptake of DENV by mononuclear cells. DENV then replicates in these macrophages thereby increasing viral production. The uptake of the heterotypic antibody-virion complex occurs after the docking of the immune complex to the Fcγ-R of a mononuclear cell expressed on its surface[18]. Recently, dengue viral load at presentation and the odds of severe disease were highest among patients with low to intermediate pre-infection antibody titers and lowest among those with the highest antibody titers[19].

The role of antibodies against NS1 is still matter of discussion. On the one hand, passive transfer of anti-DENV-NS1 antibodies to mice has proven to avoid lethal encephalitis[20]. Antibodies that bind sNS1 in circulation were shown to neutralise its vasoactive effects, as demonstrated in a mouse model of NS1-induced vascular leakage[12]. On the other hand, human antibodies against NS1 may react against human endothelial cells[21], platelet antigens[22] and anticoagulation factors[23]. Human antibodies against NS1 can also consequently produce vascular leakage, thrombocytopenia and coagulopathy, possibly as a consequence of NS1 mimicry effect.

Clinical symptoms

In 2009, the WHO changed the definition of dengue infection. Symptomatic dengue can present as undifferentiated fever, dengue and severe dengue. Asymptomatic dengue could represent at least approximately 10% of infected patients[24]. The main symptom in dengue is fever, usually higher than 38°C, reaching in many patients 40°C and lasting 3-7 days. Myalgia, joint pain, retroocular pain, sore throat and facial erythema could also be present. Dengue can present with alarming signs: abdominal pain, persistent vomiting, clinically evident fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement > 2 cm, increased hemoconcentration concurrent with platelet decline[25]. Alarming signs indicate the need for patient hospitalization to avoid severe complications. Severe dengue can present as severe plasma leakage, severe bleeding or severe organ involvement[25].

After the mosquito bite there is a period of up to 7 days of incubation without clinical symptoms. The febrile period lasts between 4-7 days and is followed by the critical period. This period lasts approximately 2 days and is characterized by defervescence (decrease in body temperature), hemoconcentration and decrease of platelet count. The recovery phase is the last period and is characterized by the return of plasma to the vasculature with near normal hematocrit values.

Diagnosis of dengue infection

Approximately 24 to 48 h before the febrile period there is already detectable viremia which lasts till the start of the critical period. During viremia either RNA or antigen detection methods could be used for the diagnosis of Dengue infection. The CDC and the WHO recommend RT-PCR for the diagnosis of dengue disease, during this period. After the febrile period, the diagnosis is based on the detection of specific IgM and IgG antibodies[1, 25].

Ocular manifestations of dengue

Anterior manifestations

Subconjunctival hemorrhages are the most frequent ocular sign reported by patients with dengue infection. Up to 37,3% of patients with thrombocytopenia presented it during the critical period[26]. Diffuse epithelial keratitis as well as stromal keratitis has been reported in patients with acute dengue infection[27]. Necrotizing scleritis was observed in a Japanese patient without precedent autoimmune diseases who became infected with dengue virus during holidays in the Philippines[28]. The patient's scleritis was controlled with methylprednisolone pulse-therapy. There were no further recurrences after treatment, but the patient developed scleral thinning over the following years.

Table 1. Uveitis caused by dengue virus infection. Clinical presentations reported frequencies and response to treatment.

Uveitis	Clinical presentation	Frequency	Response to treatment
Anterior	Unilateral or bilateral Predominantly non-granulomatous	Frequent after the recovery period, up to 5 months	Good response to topical corticosteroids
Intermediate	Associated with dengue maculopathy	Rare	Insufficient data
Posterior	Retinal vasculitis	Frequent	Good response to systemic corticosteroids Final visual acuity varies according to lesion in the outer retinal layers
	Exudative retinal detachment	Frequent	
	Multifocal chorioretinitis	Less frequent	
	Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)		
	Choroiditis		
	Acute zonal occult outer retinopathy (AZOOR)		
	Neuroretinitis (macular star)	Rare	

Other anterior manifestation of dengue infection is acute angle closure glaucoma (AAG). AAG associated with dengue can present with unilateral or bilateral involvement[29]. This entity may be associated with extensive choroidal effusions[30] or as a consequence of an iris plateau configuration[31].

Patients presenting with ocular pain, eye redness and photophobia few weeks or months after acute dengue fever are frequently diagnosed with presumed dengue associated anterior uveitis[32]. Anterior uveitis (AU) is less frequently diagnosed during acute disease[33]. AU can present as unilateral or bilateral uveitis, more frequently as non-granulomatous uveitis[34]. The etiological mechanism seems to be an autoimmune reaction following dengue infection since the patients respond to topical or periocular corticosteroids.

Posterior manifestations

Intermediate uveitis is an infrequent presentation of dengue infection. In a series of 65 eyes of patients with visual complains associated with dengue infection only 8 had intermediate uveitis[35]. Approximately 11% of patients who experience dengue maculopathy, a frequent clinical presentation of dengue infection, also have signs of intermediate uveitis[36].

Posterior uveitis (PU) is a common complication of dengue infection. PU by dengue is one of the three more frequent aetiologies of posterior uveitis in Singapore[37]. Clinical presentations of PU in dengue comprise vascular retinitis, exudative retinal detachment, chorioretinitis and neuroretinitis (Table 1). In a study that included 41 patients, 15 of 65 eyes with posterior ocular manifestations had retinal vasculitis[38]. Other retinal signs associated with retinal vasculitis are intraretinal hemorrhages and exudative retinal detachment[39-40]. Exudative retinal detachment was observed in 13 of those 15 previously mentioned eyes with severe retinal vasculitis in the study published by Theo SC. In severe cases of retinal vasculitis retinal ischemia may be present due to microvascular occlusion[41]. When the macular retinal detachment has fibrinous material a pseudophypopion can be observed as that reported in two patients from Malaysia[42].

Multifocal areas of chorioretinitis with retinal vasculitis, retinal hemorrhages and exudates were described by Tabbara K in 2 patients from Saudi Arabia[43].The patients had leukopenia and throm-

bocytopenia with high titers of IgM anti-dengue. The healing of the lesions left discrete atrophic chorioretinal scars with nummular shapes. Chorioretinal lesions during dengue infection may display features in the spectrum of acute posterior multifocal placoid pigment epitheliopathy (APMPPE)[44] or choroiditis[45]. Multifocal chorioretinal lesions resembling APMPPE were described in a patient who developed dengue fever after visiting the Caribbean islands. The OCT revealed disruption of the ellipsoid layers and RPE. The healing of the lesion left discrete chorioretinal scars[44]. Severe decrease in visual acuity and persistent scotoma in patients with dengue infection were associated with disruption of the outer neurosensory retina involving the outer limiting membrane, the myoid and ellipsoid zone as well as the outer segments of the photoreceptors, findings similar to those described in acute zonal occult outer retinopathy, AZOOR[46-47].

Concomitant inflammation of the optic nerve and macula can manifest as neuroretinitis. A classical presentation of neuroretinitis with vitritis, papillitis, exudates forming a macular star was reported in a Brazilian patient with acute dengue fever[48].

Two reports of blinding panophthalmitis in patients with severe dengue were recently described[49-50]. In both cases, the patients were admitted to hospital. They developed panophthalmitis due to secondary bacterial infection (Staphylococcus epidermidis and Bacillus Cereus). Both patients survived but the infected eyes were eviscerated.

Clinical spectrum of dengue maculopathy

Dengue maculopathy is the most frequent cause of visual complains in patients with dengue infection. Approximately 10% of infected patients admitted to hospitals will develop dengue maculopathy (DM)[51] or complain of blurry vision[52]. Main visual symptoms are blurry vision and or scotomata[51]. Decrease of visual acuity (VA) typically appears during the critical period, but it can also present up to 30 days after the febrile period. Other less frequent symptoms are myodesopsia and metamorphopsia. The decrease in VA at the time of diagnosis is mild to moderate in most patients. Approximately 69% of patients had a VA of 20/200 or better according to Teoh *et al*[35]. Bilateral involvement is very frequent but usually asymmetrical[35-36]. The triad of photopsia, myodesopsia and blurry vision was highly predictive of retinal hemorrhages[52].

According to its pathogenesis and ordered by frequency: macular edema, macular retinal detachment + severe vasculitis, macular hemorrhage and foveolitis are the most frequent clinical presentations of DM[42]. In a small case series, Chan *et al* found that macular hemorrhages were the most frequent cause of decreased visual acuity followed by retinal vasculitis and macular retinal detachment[33].

Three different patterns were described in DM using standard optical coherence tomography (OCT): diffuse retinal edema, cystoid retinal edema and foveolitis (Table 2). The latter is characterized by a thickening and hyperreflectivity of the subfoveal outer retinal layers[38].

The use of OCT angiography (OCTA) in patients with foveolitis and outer maculopathy shows flow deficit of the superficial retinal capillary plexus in 43,75% of the patients. Areas with flow deficit in the deep retinal capillary plexus were present in all patients. None of the eyes showed presence of choriocapillaris flow deficit areas[53].

Recently a new clinical presentation involving the macular neuroretina during dengue disease was described. Acute macular neuroretinopathy (AMN) is characterized by ischemia of the retinal deep capillary plexus (DCP)[54]. Clinically, retinal exudation can present around the foveal area. Macular retinopathy can be accompanied by vitritis and by optic nerve inflammation. Fluorescein angiography may show vascular leakage in the macular area and optic disc staining in the late phase. The OCTA displays involvement of the different vascular retinal plexus but only the deep retinal capillary plexus are associated with the disruption of the IS/OS junction of the retina, a typical finding in optical coherence tomography (OCT) of AMN patients[55].

Other reported immediately after macular complication dengue infection is choroidal neovascularization[56]. Veloso *et al* described the case of a 54-year-old female patient complaining of decreased visual acuity in her left eye two weeks after dengue fever.

Table 2. Dengue maculopathy: clinical presentations and findings on fluorescein angiography (FA), optical coherence tomography (OCT) and OCT-angiography (OCTA).

Dengue maculopathy	Clinical presentation	Fluorescein-angiography (FA)	OCT pattern	OCT-A pattern
Macular edema	Diffuse macular edema	Late hyper-fluorescence. Diffuse fluorescein leakage	Diffuse retinal thickening (DRT), around central/ paracentral fovea. Loss of foveal dimple	Flow deficit in the superficial capillary plexus
	Cystoid macular edema	Hyper-fluorescence due to leakage in cystoid retinal spaces in middle and late stages	Cystoid fluid spaces in the middle layers of the retina	
Exudative retinal detachment (ERD) + severe vasculitis	ERD + vasculitis Vitritis	Perifoveal fluorescein leakage and hyper-fluorescence in middle and late stages	Subretinal fluid, cystoid macular edema may also be present	Not described for dengue
Macular hemorrhage	Macular hemorrhage	Hypo-fluorescence due to fluorescence blocking in the macular area	Accumulation of fluid of medium reflectivity at the retina affecting the normal layers architecture	Not described for dengue
Foveolitis	White yellowish dots in the fovea Mild vitritis	Perivascular foveal leakage and blockage of arteriolar fluorescence	Hyper-reflectivity at the outer plexiform and outer nuclear layers	Flow deficit in the superficial and deep capillary plexus
Acute macular neuroretinopathy (AMN)	Exhudation around vessels of macular area	Fluorescein vascular leakage around the macular vessels. Optic disc staining in late phase	Disruption of the IS/OS junction in the outer retina	Flow deficit in the 3 capillary plexus, low VA is associated with flow deficit of the deep capillary plexus

A diagnosis of classic CNV was made with FA and confirmed with SD-OCT. The patient was treated with ranibizumab intravitreal injections reaching a BCVA of 20/20 after the treatment.

Neuro-ophthalmological manifestations

Approximately 97% of patients with dengue fever will complain of headaches[57]. Neurological signs upon dengue infection are reported in only 1% to 5% of patients[58] and neuro-ophthalmic manifestations are rare or infrequent[59]. Nevertheless, in the clinical history of 2 out of the 3 patients described below, who sought ophthalmic consultation during the 2020 epidemic in Misiones, the primary ocular manifestation was neuro ophthalmological. Encephalitis and dengue encephalopathy are the most frequent neurological manifestations, followed by Guillain-Barré syndrome and nerve palsies. Abducens nerve palsies (VI nerve palsy) is a frequent form of nerve palsies associated with dengue infection. Abducens palsies as well as the above mentioned neurological manifestations are more frequent during the critical period[60-62]. Optic neuritis was reported to occur in 0.1% to 1.5% of patients with dengue infection[35]. It could present as either inflammation of the optic disc or as retrobulbar optic neuritis[63-64]. Recently, Lana-Peixoto *et al* reported two cases of neuromyelitis optica spectrum disorder (NMOSD) in patients positive for serum AQP4-antibody suggesting that dengue infection may trigger seropositive NMOSD[65].

Treatment

Good resolution of anterior mild inflammatory manifestations may be achieved with topical corticosteroids such as in mild to moderate anterior uveitis[66]. Local periocular treatment (sub-Tenon's triamcinolone injection) can be used in severe forms of unilateral anterior uveitis and mild cases of dengue retinopathy. The use of intravitreal triamcinolone can be considered in patients with unilateral maculopathy[36].

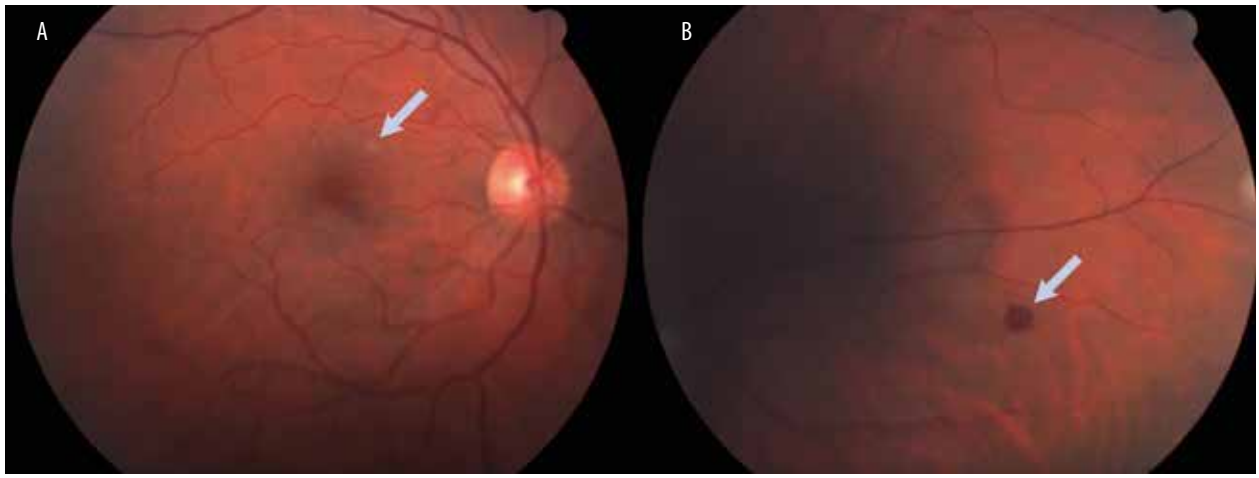

Figure 1. (A) Small yellowish retinal lesion in the inferior area of the macula outside the fovea (arrow). (B) Retinal hemorrhage in the nasal area of the right eye (arrow).

Systemics corticosteroids are needed in severe scleritis and in posterior manifestations where immune mediated mechanisms are suspected (retinal vasculitis, AMN and foveolitis). In patients whose visual acuity was lower than 20/100, methylprednisolone pulse therapy (1 g/day) was efficient in the treatment of severe posterior uveitis and optic neuritis. Pulse therapy should be followed by oral prednisone with slow tapering.

There are few reports of severe PU and dengue maculopathy patients with VA lower than 0.1 treated with intravenous Immunoglobulin (0,4 g/kg/ day) for 3 days. Visual acuity was restored to 0.5 after 15 days of treatment[67].

Despite the fact that anti-VEGF therapy had shown to restore vascular permeability in macular edema associated with retinal vasculopathy, there are no reports regarding its use in dengue maculopathy except for choroidal neovascularization[56]. The use of such well-known agents could be hypothetically useful, specially in macular edema caused by dengue infection.

Ocular findings in patients examined during the 2020 dengue epidemic

Case 1 (retroorbital pain-normal vision)

A 42 years old man seeks consultation due to retroocular pain. He has been diagnosed dengue fever by a medical doctor specialized in tropical medicine. He suffered high fever, asthenia and myalgia for 5 days. He is in the recovery phase but still complains of bilateral retroocular pain. A diagnosis of dengue is suspected based on the symptoms and a positive antigen NS1 ELISA test. His best corrected visual acuity (BCVA) was 20/20 in both eyes. The patient had normal pupillary reflexes and ocular movements. There were no anterior signs of ocular inflammation. Intraocular pressure was 16 mmHg in both eyes. There were scattered retinal hemorrhages outside the posterior pole in both eyes (Fig. 1). A small, yellow, well-defined deep retinal dot like those described in foveolitis was observed in the superior part of the macula, outside the fovea, in the right eye (Fig. 1). The patient received no treatment and was controlled 15 days later dengue disease was confirmed by the presence of anti DENV positive IgM and IgG results. Resolution of the hemorrhages and the macular spot was confirmed after 3 months of the initial examination.

Case 2 (severe unilateral decrease in visual acuity)

A 38-year-old male patient seeks ophthalmic consultation as an outpatient in a private clinic. He complains of decrease in visual acuity in the left eye for the last 3 days accompanied by pain when moving the eye. Three weeks before he had 4-day episode of fever, malaise and headaches. He also

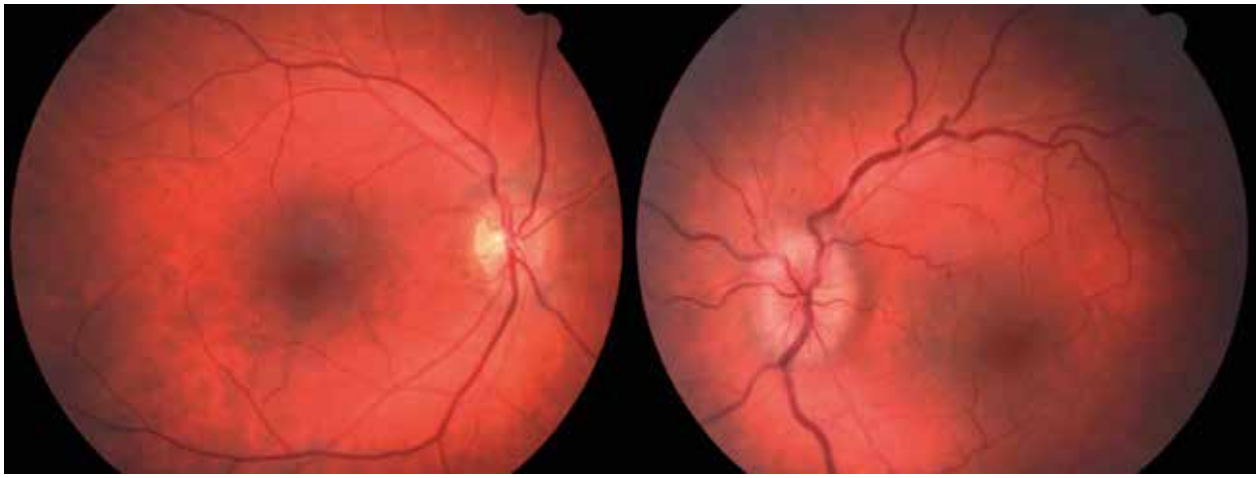

Figure 2. Images of the right and left posterior fundus of the eye. The right optic disc and macular area appears normal. The left optic disc has diffused borders with exudative changes that together with the clinical presentation of the patient led to the diagnosis of left optic neuritis.

referred a history of relatives with dengue infection. BCVA was 20/20 in the right eye and counting fingers on the left eye. There was a RAPD in the left eye and severe decrease in the chromatic vision. The anterior biomicroscopy was normal as well as the intraocular pressure in both eyes. The fundus of the eye revealed a left optic disc with diffuse borders and inflammation (Fig. 2). There were no signs of retinopathy. The right eye fundus was normal. Routine lab exams (hematocrit, ESD, kidney and liver function assays) as well as an MRI with gadolinium of the CNS and serology for dengue, syphilis and toxoplasma gondii were ordered. The patient did not want to receive corticosteroid pulsetherapy in a hospital, due to the COVID-19 pandemic, so he started oral meprednisone 1mg/kg/day as an outpatient. The CNS MRI results, and the routine lab exams were normal. VDRL and serology for syphilis were negative. A positive IgM and IgG anti-DENV was detected. Serology for toxoplasma gondii indicated a chronic infection, a regular finding in an adult patient from Misiones. The patient visual acuity started to improve daily. After 4 weeks of treatment the patient attained 20/20 vision on the left eye and his visual fields were normal.

Case 3 (abducens nerve palsies)

A 42 years old man seek consultation at the emergency room. He complained of dysesthesia in his lower extremities, dysarthria and diplopia for the last 48 h. He had fever, myalgia and gastrointestinal symptoms for the last 10 days. He explains that due to the SARS-Cov2 pandemic intercurrence he received telephonic assessment and was prescribed paracetamol. The clinician that examined him in the emergency room ordered routine blood laboratory test (hematocrit, WBC count, ESR, PCR, liver and kidney function laboratory tests), a Central Nervous System CAT-scan without gadolinium and an ophthalmologic examination. The CNS CAT-scan was normal. The ophthalmic examination revealed: BCVA of 20/20 in both eyes and a 30-degree esotropia in the left eye. Limited abduction of the left eye was confirmed and a left abducens nerve palsy was diagnosed. Due to his poor general health status (fever, tremors and asthenia) the patient was admitted to the hospital. A fundus examination showed performed revealing retinal exudates along the temporal vessel in the right eye and a small macular hemorrhage in the left eye. The neurologists that examined the patient ordered a CNS MRI with gadolinium and an angio-MRI. The exams revealed an acute ischemic event at the knee of the corpus callosum and also in the left cerebellum (Fig. 3). Due to the patient's signs and symptoms and the SARS-Cov-2 pandemic + dengue epidemic intercurrence, the patient was isolated and nasopharyngeal and blood samples were obtained. Seventy-two hours later the

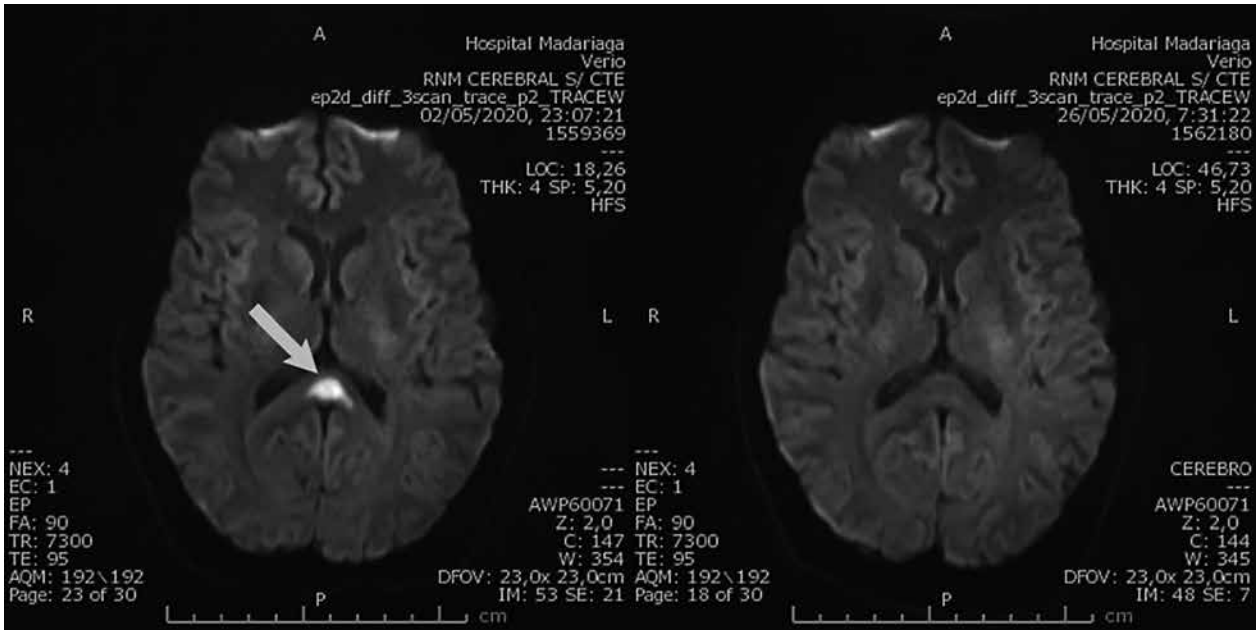

Figure 3. Central Nervous System MRI with gadolinium showing lesion in the central splenium of the corpus callosum in the diffusion-weighted imaging (image on the right). After two weeks the lesion in the corpus callosum disappeared (image on the left).

SARS-Cov-2 PCR result was negative and the NS1 for dengue was positive. No specific treatment was administered during the days of hospital admission. The neurological symptoms and ocular motor paresis improved without specific treatment. The diagnosis of dengue disease was confirmed with IgM and IgG positive serology. A diagnosis of reversible splenial syndrome (RESLES) was made based on signs and symptoms manifested by the patient, MRI images and the evolution of the patient. Although RESLES was recently described in a patient with dengue infection, this is the first case were RESLES is described with angiopathic changes in the retina.

Discussion

The ocular clinical spectrum caused by dengue infection is not random. It is influenced by the degree of vascular endothelial damage induced by the virus as well as the inflammation induced by the immune response of the host. A predominance of retinal hemorrhages and perivascular exudates in the fundus examination are an indicative of endothelial cell damage, the presence of retinal vasculitis and optic neuritis are more likely associated with a significative humoral immune response. Mechanistically it seems that early in the evolution of the disease (symptomatic and critical period), ocular and neuro-ophthalmological manifestations may be related to direct viral effects, immune mediated or due to systemic or metabolic complications (thrombocytopenia, leukopenia or hypoalbuminemia), while post-recovery and late manifestations are mainly immune mediated.

The posterior exudative and hemorrhagic manifestations are also influenced by the depth of the retinal capillary plexus disrupted. The more superficial the retinal capillary plexus affected the more superficial the exudation in the retina, resembling Purtscher-like retinopathy[68]. On the other hand, posterior deep manifestations such as foveolitis or AMN indicate the involvement of deep retinal capillary plexus. Knowledge of the retinal plexus involved is important because the alteration of deep retinal plexus is associated with disruption of the ellipsoid and interdigitation zone of the outer retina and a consequent

persistent decreased visual acuity and scotoma as described in AMN[55]. Together, the results indicate a relevant role of OCTA in the diagnosis of the retinopathy upon dengue infection.

Endothelial damage and vascular leakage are the main pathogenetic mechanism during the first two weeks of the disease while immunological mechanism may persist for few months. After an extensive search in the online clinical databases only one publication of chronic uveitis was associated with dengue infection. Recently, however, in a population based cohort study dengue infection was associated with the development of a higher frequency of autoimmune diseases. The list of diseases included known etiology for anterior uveitis (Reiter's syndrome) and posterior or diffuse uveitis (systemic vasculitis) as well as optic neuritis (multiple sclerosis)[69].

Despite our limited experience with the disease, the review of dengue epidemics, including the 2020 dengue epidemic in Misiones, taught us valuable lessons: 1) patients with dengue infection may be visually asymptomatic but still present retinal changes, while the disease is not affecting the fovea. Also, afebrile or asymptomatic dengue infected patients may develop exudative or inflammatory ocular manifestations, so dengue infection should be ruled-out if clinical ocular signs are compatible with dengue diagnosis. 2) The use of new technologies such as SD-OCT and OCTA can help in the diagnosis of the retinopathy and follow up of patients. 3) Neuro-ophthalmological signs may not be that infrequent as described. Two out of the 3 patients that seek ophthalmologic examination and were examined by the authors, had neuro-ophthalmological manifestations. 4) Immune mediated ocular manifestations such as anterior uveitis, retinal vasculitis and optic neuritis may appear few weeks or months later after the critical period of the disease. 5) The treatment of posterior uveitis and dengue maculopathy has been limited to corticosteroids and intravenous immunoglobulin. Clinical studies using agents known to restore vascular permeability such as bevacizumab, ranibizumab and aflibercept can be projected to evaluate its clinical use in dengue maculopathy as additional treatments.

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