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 retinianas 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 uveíte 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 testar drogas con conocida actividad estabilizadora de la permeabilidad vascular retinal y también de drogas antivirales.

**Palabras clave:** dengue, infecciones oculares.

### Introduction

Dengue virus (DENV) belongs to the *Flaviviridae* virus family. It is an arbovirus, an arthropod borne virus, 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.

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.

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. According to the National Health Ministry, Argentina has more than 92,229 dengue suspected cases since week 31 of 2019 (end of July 2019). 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 epidemic of dengue in Argentina. Current prevalent serotypes in Argentina are DENV-1 in the northwest, DENV-1 and DENV-4 in the center and DENV-1, DENV-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 DENV-2, 5 for DENV-3 and 4 genotypes for DENV-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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{12}. On the other hand, human antibodies against NS1 may react against human endothelial cells\textsuperscript{21}, platelet antigens\textsuperscript{22} and anticoagulation factors\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{26}. Diffuse epithelial keratitis as well as stromal keratitis has been reported in patients with acute dengue infection\textsuperscript{27}. Necrotizing scleritis was observed in a Japanese patient without precedent autoimmune diseases who became infected with dengue virus during holidays in the Philippines\textsuperscript{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.
Other anterior manifestation of dengue infection is acute angle closure glaucoma (AAG). AAG associated with dengue can present with unilateral or bilateral involvement. This entity may be associated with extensive choroidal effusions or as a consequence of an iris plateau configuration.

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. Anterior uveitis (AU) is less frequently diagnosed during acute disease. AU can present as unilateral or bilateral uveitis, more frequently as non-granulomatous uveitis. 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. Approximately 11% of patients who experience dengue maculopathy, a frequent clinical presentation of dengue infection, also have signs of intermediate uveitis.

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. 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. Other retinal signs associated with retinal vasculitis are intraretinal hemorrhages and exudative retinal detachment. 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. When the macular retinal detachment has fibrinous material a pseudophypopion can be observed as that reported in two patients from Malaysia.

Multifocal areas of chorioretinitis with retinal vasculitis, retinal hemorrhages and exudates were described by Tabbara K in 2 patients from Saudi Arabia. The patients had leukopenia and throm-
bocytopenia con altos títulos de IgM anti-dengue. La curación de las lesiones hizo que quedaran marcas chorioretinales atroficas en forma de placas. Las lesiones chorioretinales durante la infección de dengue pueden exhibir características en el espectro de la acute posterior multifocal placoid pigment epitheliopathy (APMPPE)44 o choroiditis45. Lesiones chorioretinales multifocales que se parecían a APMPPE se describieron en un paciente que desarrolló fiebre de dengue después de visitar las Islas del Caribe. La OCT reveló la discontinuidad de las capas elípticas y RPE. La curación de la lesión dejó marcas chorioretinales44. La severa disminución en la agudeza visual y el persistente scotoma en pacientes con infección de dengue fueron asociadas con la discontinuidad de la retina neurosensorial externa, incluyendo la membrana limitante externa, la myoid y el zángano elíptico así como las segmentos de los receptores fotorreceptores, los hallazgos similares a aquellos descritos en la acute zonal occult outer retinopathy, AZOOR46-47.

La inflamación concurrente del nervio óptico y la macula puede manifestarse como neuroretinitis. Una presentación clásica de neuroretinitis con vitritis, papillitis, exudados formando una estrella macular fue reportada en un paciente brasileño con fiebre de dengue48. Dos informes de panofthalmitis blinding en pacientes con dengue severo fueron recientemente descritos49-50. En ambos casos, los pacientes fueron admitidos en el hospital. Desarrollaron panofthalmitis debido a infección bacteriana secundaria (Staphylococcus epidermidis y Bacillus Cereus). Ambos pacientes sobrevivieron pero los ojos infectados fueron eviscerados.

**Clinical spectrum of dengue maculopathy**

La maculopatía de dengue es la causa más frecuente de quejas visuales en pacientes con infección de dengue. Aproximadamente 10% de los pacientes admitidos en el hospital desarrollarán maculopatía de dengue (DM)51 o quejan de visión borrosa52. Los síntomas visuales principales son visión borrosa y scotomata51. La disminución de la agudeza visual (VA) típicamente aparece durante el período crítico, pero también puede presentarse hasta 30 días después del periodo febril. Otros síntomas menos frecuentes son myodesopsia y metamorfopsia. La disminución en la VA al momento del diagnóstico es leve a moderada en la mayoría de los pacientes. Aproximadamente 69% de los pacientes tuvieron un VA de 20/200 o mejor según Teoh et al55. Involucro bilateral es muy frecuente pero generalmente asimétrico35-36. El triángulo de la fotosensibilidad, myodesopsia y visión borrosa fue altamente predictivo de hemorragias retinianas52.

Según su patogenia y ordenado por frecuencia: macular edema, macular retinal detachment + severa vasculitis, hemorragia macular y foveolitis son las presentaciones clínicas más frecuentes de DM42. En un estudio de serie pequeño, Chan et al encontraron que las hemorragias maculares fueron la causa más frecuente de disminución de la agudeza visual seguida de vasculitis maculal y macular retinal detachment33.

Tres patrones diferentes fueron descritos en DM usando OCT con técnicas OCT angiografía (OCTA) en pacientes con foveolitis y maculopatía externa mostrando un déficit de flujo del plexo capilar retiniano superficial en 43,75% de los pacientes. Areas con déficit de flujo en el plexo capilar retiniano profundo estaban presentes en todos los pacientes. Ninguno de los ojos mostraron presencia de áreas de déficit de flujo del capilar choroideo53.

Recientemente una nueva presentación clínica involucrando la neuroretina macular durante la enfermedad de dengue fue descrita. La acute macular neuroretinopathy (AMN) se caracteriza por isquemia del plexo capilar de la retina profunda (DCP)54. Clínicamente, la exudación retiniana puede presentarse alrededor de la fovea. La retinopatía macular puede acompañarse de vitritis y inflamación del nervio óptico. La angiografía de fluoresceína puede mostrar permeabilidad vascular en la macula y estación del disco económico en la fase tardía. La OCTA muestra la participación de los diferentes plexos capilares retinianos pero solo el plexo capilar retiniano profundo están asociados con la disrupción de la IS/OS junta de la retina, un hallazgo típico en la OCT de pacientes AMN55.

Otra reporte primero dengue infección de choroidal neovascularización86. Veloso et al describieron el caso de una paciente femenina de 54 años que se quejaba de disminución de la agudeza visual en su ojo izquierdo dos semanas después de la fiebre de dengue.
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\(^5\). Neurological signs upon dengue infection are reported in only 1% to 5% of patients\(^5\) and neuro-ophthalmic manifestations are rare or infrequent\(^5\). 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\(^6\). Optic neuritis was reported to occur in 0.1% to 1.5% of patients with dengue infection\(^3\). It could present as either inflammation of the optic disc or as retrobulbar optic neuritis\(^6\). 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\(^4\).

**Treatment**

Good resolution of anterior mild inflammatory manifestations may be achieved with topical corticosteroids such as in mild to moderate anterior uveitis\(^6\). 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\(^3\).
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.

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. 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
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 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 palsy)
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 ophthalmologic 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
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 where 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. 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\textsuperscript{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)\textsuperscript{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.

References

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