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DISSERTAÇÃO DE MESTRADO

CARACTERIZAÇÃO CLÍNICA DAS SÍNDROMES NEUROLÓGICAS DURANTE A TRÍPLICE EPIDEMIA DE ARBOVIROSES EM SALVADOR, BAHIA, BRASIL

MATEUS SANTANA DO ROSÁRIO

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RESUMO

INTRODUÇÃO: Os arbovírus são vírus transmitidos por vetores artrópodes e diversos deles podem ser encontrados em cocirculação no Brasil. Complicações neurológicas associadas aos vírus dengue (DENV), chikungunya (CHIKV) e zika (ZIKV) já foram descritas anteriormente na literatura. Durante a tríplice epidemia de arboviroses houve um aumento importante de casos neurológicos, principalmente síndrome de Guillain-Barré (GBS). **MATERIAL E MÉTODOS**: Iniciada uma vigilância hospitalar para síndromes neurológicas agudas, onde foram incluídos pacientes avaliados em unidades neurológicas de dois hospitais de referência em Salvador/BA durante o período de maio de 2015 a abril de 2016. **RESULTADOS**: Cinco artigos foram escritos para melhor caracterização do tema. Dois casos de GBS clássico associado ao ZIKV foram publicados durante o surto supracitado, sendo um dos primeiros artigos no Brasil relacionando as duas doenças. Foi realizada a descrição com detalhes o caso da rara síndrome opsoclonus-mioclonus encefalite (OMAS), no qual a paciente se apresentara com alteração de sensório, movimentos oculares anárquicos e ataxia. Na investigação foram detectados o DENV e CHIKV no plasma e o CHIKV no líquor pelo RT-PCR. A paciente foi tratada com corticoide venoso e teve alta com melhora funcional, sem alterações cognitivas ou motoras. Uma série de 5 casos descreveu com mais detalhe uma forma neurológica mais leve, a polineuropatia sensitiva reversível (RSP). Todos os pacientes apresentaram quadros transitórios, exclusivamente de alterações sensitivas; dois casos tinham evidência de infecção recente por ZIKV e outros 2 por CHIKV. Uma série de casos de pacientes com GBS, avaliou 14 indivíduos, sendo que 50% destes apresentavam variantes dessa doença. Havia uma maior prevalência de acometimento do nervo facial do que nas populações previamente estudadas. Prevaleceu a forma desmielinizante na eletroneuromiografia desses pacientes. Setenta e dois por cento dos pacientes foram reavaliados em 30 dias e todos tiveram ótima recuperação funcional. Por fim foi escrito um estudo de corte transversal que descreveu as síndromes neurológicas ocorridas em Salvador durante o surto da tríplice arboviral com 29 pacientes acompanhados; aproximadamente 50% se apresentaram com GBS ou suas variantes. Outras manifestações como encefalites, mielites, OMAS e RSP foram descritas. Cerca de 80%

dos pacientes apresentavam evidência sorológica de infecção recente por ZIKV ou CHIKV. **CONCLUSÃO**: Foram descritas manifestações neurológicas como GBS e outras síndromes relacionadas às arboviroses. O melhor conhecimento dessas manifestações pode trazer benefício para prevenção, diagnóstico e tratamento dessas doenças, assim como melhorar as ações em saúde pública para combate às complicações por arboviroses.

Palavras-chaves: Zika, Chikungunya, Dengue, Manifestações Neurológicas, Síndrome de Guillain-Barré, Encefalite, Mielite, Opsoclonus-Mioclonus-Ataxia

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ABSTRACT

INTODUCTION: Arboviruses are viruses transmitted by arthropod vectors and several of them can be found in cocirculation in Brazil. Neurological complications associated with dengue virus (DENV), chikungunya (CHIKV) and zika (ZIKV) have previously been described in the literature. During the triple epidemic of arboviruses there was a significant increase in neurological cases, mainly Guillain-Barré syndrome (GBS). **MATERIAL AND METHODS**: A hospital surveillance for acute neurological syndromes was started, which included patients evaluated in neurological units of two reference hospitals in Salvador / BA during the period from May 2015 to April 2016. **RESULTS**: Five articles were written to better characterize the clinical manifestations. Two cases of classic GBS associated with ZIKV were published during triple arbovirosis outbreak, being one of the first articles in Brazil correlating the two diseases. A detailed description was made of the rare opsoclonus-myoclonus encephalitis syndrome (OMAS), in another article, in which the patient presented with confusion, anarchical ocular movements and ataxia. DENV and CHIKV were detected in plasma and CHIKV in the CSF by RT-PCR. The patient was treated with venous corticosteroids and was discharged with functional improvement, without cognitive or motor alterations. A series of 5 cases described a milder neurological form, the reversible sensory polyneuropathy (RSP). All patients presented only with transient sensory disturbances; two cases evidenced recent infection by ZIKV and another 2 by CHIKV. A case-series of GBS patients evaluated 14 individuals, with 50% of them presenting with GBS subtypes. There was a higher prevalence of facial nerve involvement than in the previously studied populations. The demyelinating form prevailed in the electroneuromyography studies of these patients. Seventy-two percent of the patients were reassessed in 30 days and all had an optimal functional recovery. Finally, a cross-sectional study was written and described the neurological syndromes that occurred in Salvador during the outbreak of the triple arboviral with 29 patients followed up; approximately 50% presented with GBS or its subtypes. Other manifestations such as encephalitis, myelitis, OMAS and RSP were described. About 80% of the patients had serological evidence of recent infection by ZIKV or

CHIKV. **CONCLUSION**: Neurological manifestations such as GBS and other syndromes related to arbovirus have been described. The better knowledge of these manifestations can benefit the prevention, diagnosis and treatment of these diseases, as well as to improve the actions in public health to combat complications by arbovirosis.

Key word: Zika, Chikungunya, Dengue, Neurological Manifestations, Guillain-Barré Syndrome, Encephalitis, Myelitis, Opsoclonus-Myoclonus-Ataxia

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LISTA DE ABREVIATURAS E SIGLAS

ADEM	Acute disseminated encephalomyelitis/ encefalomielite disseminada aguda
AIDP	Acute inflamatory demyelinating polyneuropathy
AMAN	Acute motor axonal neuropathy
ATP	Acute transiente poluneuritis/ Polineurite transitória aguda
CHIKV	Chikungunya vírus
CSF	Cerebrospinal fluid
DENV	Dengue vírus
DNA	Desoxiribonucleic acid
ECSA	East/Central/South African Genotype
EMG	Electromyography/ eletroneuromiografia
FIFA	Federação internacional de futebol
FP	French Polynesia/ Polinésia Francesa
GBS	Guillain-Barré syndrome/ síndrome de Guillain-Barré
HBS	House-Brackmann scale
HFS	Hughes Functional scale
IOL	Indian Ocean Lineage
IVIG	Imunoglobulina humana venosa
CSF	Cerebrospinal fluid/ Líquido cefalorraquidiano
MAYV	Mayaro vírus
OMAS	Opsoclonus myoclonus ataxia syndrome
ONNV	O'nyong nyong vírus
OROV	Oropouche vírus
RNA	Ribonucleic acid
RNM	Ressonância nuclear magnética
RSP	Reversible sensory polineuropathy/ polineuropatia sensitiva transitória
RT-PCRq	Real time polymerase chain reaction
SC ZIKAV	Síndrome congênita relacionada ao zika vírus
USUV	Usutu vírus
WNV	West Nile vírus
ZIKV	Zika vírus

SUMÁRIO

1. INTRODUÇÃO

Os arbovírus são vírus transmitidos por vetores artrópodes (MUSSO; CAO-LORMEAU; GUBLER, 2015). Incluem-se nessa classificação diversos vírus de RNA, dentre eles os alfavírus, flavivírus, bunyavírus, nairovírus, flebovírus, orbivírus, vesiculovírus e togotovírus; e apenas um vírus de DNA que é o vírus da febre suína africana (asfarvírus) (WEAVER; REISEN, 2010). Uma variedade de vírus pode ser encontrada em circulação no Brasil, vistos em diversos estudos de soro-prevalência e vigilância de doenças exantemáticas (NUNES et al., 2009). No Brasil, diversos desses arbovírus circulam em áreas urbanas e peri-urbanas como vírus da dengue (DENV), chikungunya (CHIKV) e zika (ZIKV); outros causando surtos de doença exantemática febril em regiões específicas como Oropouche (OROV), mayaro (MAYV) e febre amarela (YFV) (BATISTA et al., 2012).

O Zika vírus (ZIKV) é um arbovírus da família da febre amarela (flavivírus) descrito pela primeira vez, isolado de um macaco Rhesus durante a investigação de casos de febre amarela, na floresta Zika, em Uganda na África, em 1947 (MUSSO; CAO-LORMEAU; GUBLER, 2015).

A primeira identificação do ZIKV em humanos foi em 1952 (DICK, 1952) porém a primeira descrição de doença ocorreu em 1954 (MACNAMARA, 1954). Durante anos, houve identificação sorológica do vírus em pesquisas de vigilância na África e Ásia, porém sem nenhuma epidemia identificada até 2007, quando um surto ocorreu nas ilhas Yap, dos Estados Federados da Micronésia (DUFFY et al., 2009). Durante esse evento houve uma estimativa de 73% de taxa de infecção pelo ZIKV. Não houve registros de complicações neurológicas naquele período.

Em 2013, na Polinésia Francesa, cerca de 11% da sua população fora infectada (28.000 casos) pelo ZIKV (MUSSO; NILLES; CAO-LORMEAU, 2014). Houve aumento no número de casos de síndrome de Guillain-Barré (GBS) associada ao aumento de casos de infecção por ZIKV nesse território durante esse período (IOOS et al., 2014).

Anos depois houve uma rápida disseminação do ZIKV através do oceano pacífico até a chegada no continente americano em 2014 através do Chile (Polinésia Francesa (PF), Nova Caledônia, Ilhas Cook, Ilha de Páscoa, Chile) (IOOS et al., 2014).

Em 2015, o Brasil enfrentou um surto de ZIKV de grandes proporções (CAMPOS; BANDEIRA; SARDI, 2015). No final de 2015, 66.203 casos suspeitos de zika foram notificados na Bahia (BAHIA, 2016); associado a esse fato, foi observado aumento do número de casos de complicações neurológicas na Bahia, com 177 casos de doenças neurológicas associadas, sendo que 67 (37,85%) foram confirmadas como SGB e outras 49,7% ainda

permanecem em investigação ou aguardando a correlação com a doença viral prévia (BAHIA, 2016).

No Brasil, em 2015, houve um grande número de casos de complicações neurológicas associadas ao ZIKV, principalmente SGB e síndromes congênitas com manifestações de microcefalia, aumentando a preocupação relacionada a arbovírus no nosso território ("Zika Virus in the Americas — Yet Another Arbovirus Threat — NEJM", [s.d.]).

O CHIKV, da família dos alfavírus foi descrita inicialmente em 1952 na África e sua disseminação para outros países aconteceu principalmente após 2005 quando houve um grande número de casos nas Ilhas Reunión (CAMPION; WEAVER; LECUIT, 2015). Sua chegada no Brasil ocorreu em 2014 e sua disseminação foi rápida principalmente nos estados do nordeste (NUNES et al., 2015a). Diversas manifestações neurológicas foram descritas principalmente durante a epidemia nas Ilhas Reunión, como GBS, encefalites, meningites e mielites (GÉRARDIN et al., 2015). No Brasil, diversas manifestações neurológicas, incluindo GBS, mielite, encefalomielites, miosites, dentre outras, foram descritas em uma série de casos (MEHTA et al., 2018). Há de se alertar para outras complicações graves não-neurológicas como alterações cardíacas, choque, dentre outras, que podem decorrer da infecção pelo CHIKV (CAMPION; WEAVER; LECUIT, 2015; NUNES et al., 2015b).

O DENV que circula no Brasil desde 1845 é uma das principais doenças com grande impacto de saúde pública no país, com sucessivas epidemias e cocirculação de 4 sorotipos (DEN1 – DEN4) desde 2010 (FARES et al., 2015). Manifestações musculares (miosite, rabdomiólise), desmielinizantes (SGB), encefalites, mielites e meningite, são exemplos de complicações descritas na literatura mundial, porém essas manifestações neurológicas mais graves são incomuns a despeito da grande disseminação desta doença (CAROD-ARTAL et al., 2013).

Apesar da grande prevalência de dengue no mundo, as manifestações neurológicas relacionadas a este vírus são incomuns, porém podem ser potencialmente graves. Manifestações graves como meningites ou encefalites, incrementam o risco de morte em pacientes com manifestações de infecção por DENV, por isso deve-se estar atento a alterações neurológicas compatíveis com tais complicações (ARAÚJO et al., 2012).

Devido à nova situação de circulação de três vírus de manifestações clínicas semelhantes e com potenciais de complicações graves, é de suma importância o estudo e reconhecimento das manifestações clínicas destes pacientes.

Desta forma, propôs-se a realização de uma vigilância hospitalar para síndromes neurológicas agudas, com intuito de identificar os casos surgidos durante a epidemia e caracterizá-los clínica e laboratorialmente. Cinco diferentes publicações surgiram como

resultados desta vigilância: um estudo de corte transversal para descrever as diferentes síndromes neurológicas ocorridas em Salvador durante o surto da tríade arboviral; uma série de casos descrevendo as manifestações neurológicas da SGB e seus subtipos, e fazer um paralelo com infecção por ZIKV, CHIKV e DENV; uma série de casos para descrever formas neurológicas mais leves (polineurite transitória aguda – PTA) relacionadas a infecção prévia por arbovírus; uma descrição de caso clínico de uma doença neurológica rara (opsoclonus-mioclonus-ataxia) com confirmação por RT-PCRq para CHIKV e DENV4 e a descrição clínica de 2 casos de SGB com confirmação sorológica para ZIKV, que figura dentre os primeiros casos publicados no Brasil.

2. REVISÃO DE LITERATURA

2.1 INTRODUÇÃO

Os vírus transmitidos biologicamente entre vertebrados por insetos artrópodes, sejam eles mosquitos ou carrapatos, são chamados de arbovírus. Para que os vírus sejam classificados dessa maneira é necessário que os mesmos repliquem dentro desses vetores (WEAVER; REISEN, 2010).

Inúmeros são os arbovírus conhecidos, e deles nos últimos séculos, cinco são reconhecidamente disseminados em ambos os hemisférios mundiais: DENV, YFV, vírus do Nilo ocidental (WNV), CHIKV e ZIKV. Diversos outros arbovírus causam surtos em diferentes áreas do globo, porém não são disseminados tão amplamente quanto os vírus supracitados, como os vírus da encefalite japonesa (JEV), vírus da encefalite de Saint Louis (SLEV), vírus O'nyong nyong (ONNV), vírus da encefalite do vale Murray (MVEV), vírus da encefalite do vale Rift (RVEV) e vírus Usutu (USUV) (GOULD et al., 2017).

Muitos desses vírus supracitados são reconhecidamente relacionados a doenças neurológicas como o WNV, SLEV, EJV. Os vírus DENV, ZIKV e CHIKV, recentemente em cocirculação no Brasil, são conhecidos como causando doenças exantemáticas leves ou síndromes febris agudas, porém diversos relatos mostram que os mesmos podem cursar com complicações graves, incluindo alterações neurológicas como SGB, encefalites, mielites, dentre outras (CAROD-ARTAL et al., 2013; PINHEIRO et al., 2016).

2.2 DENGUE VÍRUS

O DENV é um vírus de RNA, membro do gênero *Flavivírus* na família Flaviviridae, transmitido aos seres humanos através da inoculação pelos mosquitos do gênero *Aedes*. Quatro sorotipos cocirculam no Brasil desde 2010 (DENV1-DENV4), e podem ter cursos de infecção desde assintomático, perpassando pela manifestação mais comum de doença exantemática febril autolimitada, até cursando com doença mais grave, podendo ser fatal (FARES et al., 2015).

O DENV circula no Brasil desde 1845, registrado inicialmente no estado do Rio de Janeiro. O programa de erradicação do mosquito *Aedes aegypti* funcionou adequadamente, deixando o país livre desse vetor até o ano de 1976. Em 1981 devido a re-infestação de áreas peri-urbanas do Brasil pelo *Ae. Aegypti*, ocorreram novos casos em Roraima, desta vez causados pelos sorotipos DENV-1 e DENV-4. Diversos outros casos ocorreram entre 1986 e 1987 nos

estados do Rio de Janeiro, Alagoas, Ceará e Pernambuco. Durante os anos 90 houve a introdução do sorotipo DENV-2, e diversos novos surtos ocorreram em todo território nacional, com índices de incidência mais elevados nos estados da região nordeste do Brasil. O sorotipo DENV-3 foi descrito no Brasil em 2000, no estado do Rio de Janeiro, e causou um dos maiores surtos de doença em 2002. Em 2010 com a re-emergência do sorotipo DENV-4, houve um grande surto em quase todas as unidades federativas do Brasil, com a prevalência mais comum do DENV-1 (83,3%), DENV-4 (15,1%), DENV-2 (1,3%) e DENV-3 (0,3%) (TEIXEIRA et al., 2009).

Acometimento sistêmico relacionado à dengue já foi descrito em diversos estudos, incluindo manifestações cardíacas, hepáticas e neurológicas (FARES et al., 2015). As manifestações neurológicas relacionadas ao DENV também foram descritas previamente. A proporção de complicações neurológicas em estudos em que todos os pacientes com confirmação laboratorial foram avaliados, variaram de 0,5-5,3%. Pacientes com manifestações de encefalite e encefalopatia perfaziam uma proporção entre 4,6-47% de pacientes com diagnóstico de dengue em artigos anteriores (ARAÚJO et al., 2012; CAROD-ARTAL et al., 2013; FERREIRA et al., 2005; NUNES et al., 2015b; VERMA; SAHU; HOLLA, 2014).

O quadro clínico neurológico relacionado à dengue pode ser categorizado em manifestações leves e não específicos de cefaleia, tontura, desatenção, alteração discreta do sensório, agitação e insônia; manifestações mais graves como alteração de sensório, letargia, confusão mental, convulsão, meningismo, mielite, encefalite ou encefalopatia; e manifestações prolongadas como SGB, paralisia bulbar, encefalite pós-infecciosa, alteração de sensibilidade, alterações neuropsiquiátricas e síndrome opsoclonus-mioclonus-ataxia (OMAS) (VERMA; SAHU; HOLLA, 2014).

A fisiopatologia do quadro neurológico decorre de alterações secundárias a complicações sistêmicas (alterações hidroeletrolíticas, sangramento microcapilar, liberação de toxinas, alterações hepáticas ou renais); manifestações pós-infecciosas de natureza imune (SGB, amiotrofia neurálgica); ou por ação direta do vírus (encefalite, mielite, miosite) (VERMA; SAHU; HOLLA, 2014).

Encefalopatia é a manifestação neurológica mais comum relacionada à infecção por DENV. Trata-se de um termo mais abrangente para explicar alterações como sonolência, letargia, confusão mental, dentre outras. Diversas alterações sistêmicas podem acarretar encefalopatia, por isso a frequência mais alta dentre as outras complicações neurológicas. Já encefalite designa a inflamação do parênquima cerebral, usualmente relacionado a infecção. As manifestações mais comuns de encefalite são a febre associada a cefaleia, convulsões e alteração de sensório. A média de início entre a febre e alteração neurológica é em torno de 3-

7 dias. A confirmação se dá pelo quadro clínico compatível, associada a alterações em estudo do líquido céfalo-raquidiano (LCR) e a presença de indícios de infecção com as técnicas de reação de cadeia de polimerase (PCR) ou anticorpos IgM anti-DENV positivos (CAROD-ARTAL et al., 2013).

A mielite é uma manifestação rara relacionada ao DENV. O diagnóstico se faz através de clínica compatível com síndrome medular (tetraparesia ou paraparesia) e alteração de sinal na sequência T2 em ressonância nuclear magnética (RNM). Acredita-se que a mielite é decorrente da invasão direta do DENV na medula espinhal, porém já houve relatos em literatura de mielite relacionada a mielopatia pós-infecciosa, mielite transversa e encefalopatia disseminada aguda (ADEM). ADEM é uma manifestação imunomediada, que pode ser relacionada a infecção viral ou vacinação precedente. Há desmielinização do sistema nervoso central (SNC), tanto em região encefálica quanto medular. Diversas manifestações clínicas podem decorrer desta entidade, a depender da localização do SNC envolvida (encefalopatia, mielite, alterações em tronco encefálico) (VERMA; SAHU; HOLLA, 2014).

GBS é uma manifestação pós-infecciosa descrita em relatos e série de casos, pouco comumente relacionada ao DENV. Caracteriza-se por paralisia flácida aguda ascendente, que se inicia nos membros inferiores, podendo evoluir para paralisia de membros superiores, musculatura bulbar e alteração em musculatura respiratória. Sua característica laboratorial mais comum é a dissociação albuminocitológica no estudo do LCR, e estudos eletro-diagnósticos podem contribuir para melhor elucidação diagnóstica, principalmente a eletroneuromiografia (ENMG) (CAROD-ARTAL et al., 2013).

Manifestações musculares são comuns em infecção por DENV, principalmente relacionados a mialgia. Porém fraqueza de origem inflamatória muscular é incomum. Alguns casos de miosite, com elevação de creatinofosfoquinase sérica, foram relatados. Casos mais graves como rabdomiólise e miocardite já foram descritos, porém, também são incomuns relacionados ao DENV (VERMA; SAHU; HOLLA, 2014).

A OMAS é caracterizada por opsoclonus (movimentos oculares conjugados caóticos, multidirecionais) associado a mioclonia, ataxia e hipersonolência, alterações cognitivas e comportamentais. É uma síndrome rara, e na população pediátrica se apresenta como manifestação paraneoplásica relacionada ao neuroblastoma (BLAES et al., 2008). Entretanto, na população adulta, manifestações de SOMA são relacionadas a doenças infecciosas, sejam elas virais ou bacterianas. Raros casos de SOMA relacionados ao DENV já foram descritas (TAN et al., 2014).

Outras manifestações neurológicas como paralisia hipocalêmica (relacionada a distúrbios renais e hidroeletrolíticos), neuropatia isolada do nervo frênico, oftalmoplegia devido

a alteração do nervo oculomotor, neurite braquial, parkinsonismo e cerebelite, podem ser encontradas em descrições breves na literatura (VERMA; SAHU; HOLLA, 2014).

2.3 CHIKUNGUNYA VÍRUS

O CHIKV é um vírus da família dos alfavírus, um vírus de RNA inicialmente isolado em 1952-1953 na Tanzânia. Seu nome na língua Makonde significa “andar recurvado”, devido a uma das manifestações clínicas mais marcantes de sua doença, a poliartralgia intensa. A circulação do CHIKV nos primórdios envolvia um ciclo de transmissão não humano, na África subsaariana, porém no século XVIII com a facilitação do transporte de pessoas e vetores em navios na época das grandes navegações, houve o início da infecção e circulação da doença entre humanos (CAMPION; WEAVER; LECUIT, 2015).

O CHIKV tem alta taxa de infecções sintomáticas (~85%) e tem como manifestação clínica principal febre alta, rash, cefaleia, conjuntivite, poliartrite e poliartralgia importante, característica mais marcada da infecção por este arbovírus. As manifestações articulares podem estar presentes tanto na fase aguda, quanto subaguda e até mesmo crônica. Outras manifestações podem fazer parte das manifestações após a fase de febre: astenia, polineuropatia, síndrome do túnel do carpo, artrite reativa, síndrome de fadiga crônica, dentre outras (BRASIL. MINISTÉRIO DA SAÚDE. SECRETARIA DE VIGILÂNCIA EM SAÚDE. SECRETARIA DE ATENÇÃO BÁSICA, 2017).

Quatro genótipos são descritos como causando doença no mundo inteiro: oriental-central-meridional africano (ECSA), ocidental africano, que causam doenças endêmicas na África subsaariana; genótipo asiático, que circula em áreas com *Ae. Aegypti* no sudeste da Ásia; e a linhagem do oceano Índico (IOL) que causou grandes surtos na Ásia e ilhas do oceano Índico entre os anos de 2005-2011 (NUNES et al., 2015b).

A primeira introdução do vírus no ciclo urbano, após a descoberta do CHIKV em 1952, aconteceu na Índia e sudeste asiático, pelo genótipo ECSA. Depois de modificações genéticas no vírus, a linhagem asiática surgiu e perpetua a transmissão do CHIKV nessa região (entre 1953-1973). Uma nova onda de surtos ocorreu em 2004 na Ásia, provavelmente iniciada a disseminação na costa do Quênia e disseminou-se independentemente por ilhas do oceano Índico e Índia, provavelmente por viajantes de avião. A rápida disseminação nessa região pode ser atribuída a adaptação do novo genótipo IOL aos vetores *Ae aegypti e Ae albopictus*, que aumentaram a área de potencial infecção desses vírus. A disseminação do vírus continuou, com vários surtos atingindo a região sudeste da Ásia, costa da África (Ilhas Reunión - 2005-2006), chegando em 2013 à região do Caribe e chegada nas Guianas (América do Sul) com a linhagem

asiática. Nesse momento, em 2013, havia grande preocupação com a disseminação do vírus pelas Américas, pela suscetibilidade da população ao vírus (ainda não circulante na região), presença de vetores para perpetuação da infecção autóctone e falta de controle dos mesmos com políticas públicas (WEAVER et al., 2014). Em Agosto de 2015, a transmissão autóctone do CHIKV já era presente em 33 países e territórios das Américas, contando com quase um milhão de casos (CAVALCANTI et al., 2017).

No Brasil, a detecção autóctone do CHIKV foi detectada simultaneamente em 2014 na cidade de Feira de Santana (Bahia) e no Oiapoque (Amapá) (NUNES et al., 2015b). Houve rápida disseminação pelo território nacional, e em 2016, foram registrados 271.824 casos prováveis de CHIKV, com taxa de incidência de 133 casos/100.000 habitantes, distribuídos em 2.829 municípios, com a maior incidência na região nordeste (415,7 casos/100 mil habitantes) (BRASIL, 2017).

Manifestações atípicas graves podem ocorrer no curso da infecção ou após infecção por CHIKV. Dentre elas hepatites, miocardites, encefalopatia, encefalites e SGB, além de complicações e descompensação de doenças crônicas prévias (LEMANT et al., 2008).

Diversas manifestações neurológicas foram descritas em associação com o CHIKV. A patogênese parece decorrer da ativação imunomediada do hospedeiro ou da ação direta do vírus. Outra possível causa para manifestações clínicas mais graves relacionadas ao CHIKV pode ser atribuído ao potencial de descompensação de doenças crônicas prévias como insuficiência cardíaca, doença pulmonar obstrutiva crônica, insuficiência renal, dentre outras. As complicações neurológicas são raras, entretanto, nos últimos anos, tem se notado o aparecimento mais frequente dessas manifestações, devido ao aumento de número de casos de CHIKV e sua disseminação global. As manifestações neurológicas mais comuns e seu período de ocorrência estão alocados na Tabela1 (BRIZZI, 2017).

Tabela 1. Resumo das manifestações neurológicas relacionadas a CHIKV e o tempo de início com relação às manifestações virais iniciais

Manifestação neurológica	Início dos sintomas
Encefalopatia	Aguda
Encefalite generalizada	Aguda ou pós-infecciosa
ADEM	Pós-infecciosa
Rombencefalite	Pós-infecciosa
Mielopatia	Pós-infecciosa
Polineuropatia	Pós-infecciosa
Síndrome de Guillain-Barré	Pós-infecciosa
Neuropatia de nervos cranianos	Pós-infecciosa
Alterações psiquiátricas	Crônica

Modificado de: BRIZZI, K. Neurologic Manifestation of Chikungunya Virus. **Current Infectious Disease Reports**, v. 19, n. 2, 2017

Os quadros de encefalopatia são os mais comumente descritos na literatura, com aproximadamente 31% dos indivíduos acometidos por doença grave (BRIZZI, 2017). As manifestações relacionadas a esta manifestação clínica parecem ser de origem sistêmica (aumento de permeabilidade vascular, alteração hidroeletrolítica), com efeitos de edema cerebral e micro hemorragia, podendo evoluir para incapacidades graves e morte (PINHEIRO et al., 2016). As encefalites podem ter início em associação com a manifestação febril (aguda), porém também ocorrem em quadros pós-infecciosos como ADEM e rombencefalite. A apresentação clínica pode variar bastante, entretanto, alterações do sensório, convulsões e alterações focais usualmente fazem parte da apresentação clínica. Apesar de não haver relatos de OMAS associado ao CHIKV, há uma descrição isolada de mioclonia sensível aos estímulos em um paciente de 32 anos na Índia (KALITA; KUMAR; MISRA, 2013). Os casos de encefalite por CHIKV na grande epidemia das ilhas Reunión, indicaram uma incidência de 8,6 casos/100.000 habitantes, o que caracterizou o dobro de casos usualmente relatados nessa área. A taxa de letalidade desses casos foi de 16,6%, com uma proporção 30-45% de sequelas neurológicas em indivíduos acometidos por encefalite. Na Índia e ilhas do Caribe relatos mostram que uma proporção de 9-15,4% e 4%, respectivamente, de casos internados por encefalite decorrentes de infecção por CHIKV (BRIZZI, 2017).

Mielopatia e mieloneuropatia também são manifestações neurológicas descritas em casos graves de infecção por CHIKV e chegou a corresponder a 27% dos casos neurológicos em uma série de casos na Índia (CHANDAK et al., 2009). Em uma outra série de nesse país, 14% de casos de mielopatia e 12% de mieloneuropatia foram descritos em pacientes com manifestações neurológicas e infecção prévia por CHIKV (TANDALE et al., 2009). Nas Américas, um caso de mielite em um paciente que viajara para a República Dominicana foi relatado (BRIZZI, 2017).

Um aumento no número de casos de SGB foi descrito no surto de 2005-2006 nas ilhas Reunión e em 2013-2014 na Polinésia Francesa. A maioria desses pacientes foi tratada com imunoglobulina venosa humana (IVIG) e recuperaram suas funções neurológicas a longo prazo (AMRANI et al., 2007; OEHLER et al., 2015a).

No Brasil uma série de casos de 22 pacientes acompanhados no Rio de Janeiro, demonstrou uma diversidade de manifestações neurológicas além de GBS: encefalomielite, mielites, ADEM e miosite. Ainda houve em diversos casos evidência de coinfecção com o ZIKV (MEHTA et al., 2018).

Outras manifestações menos comuns entre os acometidos por complicações neurológicas após infecção por CHIKV são neuropatia em nervos cranianos, como neurite

óptica e oftalmoparesia por acometimento do nervo oculomotor, e manifestações psiquiátricas, como alterações do humor, acometimento da memória, depressão, ansiedade, síndrome de fadiga crônica e transtornos somatoformes (BRITO et al., 2016; BRIZZI, 2017).

2.4 ZIKA VÍRUS

O ZIKV é um arbovírus, da família do vírus da febre amarela (flavivírus), transmitido pelo mosquito do gênero Aedes spp. (MUSSO; CAO-LORMEAU; GUBLER, 2015). É classificado por análise de sequência em dois genótipos: o asiático e o africano (FARIA et al., 2016). Foi descrito pela primeira vez em 1947, isolado de um macaco Rhesus, durante a investigação de casos de YFV, na floresta Zika, em Uganda na África (DICK; KITCHEN; HADDOW, 1952). Apesar do ZIKV até então ser conhecido devido a pesquisas epidemiológicas na Uganda e na Nigéria, nenhuma manifestação clínica era conhecida até 1952 (MACNAMARA, 1952). Em 1954, Macnamara relatou o caso de 3 pacientes, na Nigéria com manifestações de febre, artralgia e um deles com icterícia. Nestes pacientes conseguiu-se isolar o vírus, além de positivação de sorologia contra o ZIKV através da técnica de redução e neutralização em placa (PRNT) (MACNAMARA, 1954). Mais tarde, em 1956, Bearcroft inocula o vírus em um voluntário, o qual desenvolveu um quadro de febre, artralgia e mal estar durante 7 dias, com resolução completa do quadro e sem complicações (BEARCROFT, 1956). Outros casos de infecções em humanos foram relatados: 2 chamavam atenção por descreverem a doença em pesquisadores que estavam trabalhando na região com evidência do vírus (FILIPE; MARTINS; ROCHA, 1973; SIMPSON, 1964). Diversos casos esporádicos foram descritos, principalmente na África, além da identificação de anticorpos contra o vírus em vários estudos populacionais (DARWISH et al., 1983; FAGBAMI, 1979; JAN et al., ; MOORE et al., 1975; OLSON et al., 1981, 1983; SALUZZO et al.,). Em 2006, o genoma do vírus foi decodificado (KUNO; CHANG, 2007).

Até 2007, entretanto, nenhuma doença havia sido relatada em surtos, fora do eixo África/Ásia. Neste ano, houve uma epidemia de rash cutâneo, conjuntivite, febre, artralgia e artrite nas ilhas Yap, dos Estados Federados da Micronésia. Inicialmente, acreditou-se ser manifestações relacionadas ao DENV, contudo, após análise do soro dos pacientes, foram identificados através de técnica de RT-PCR o RNA do ZIKV. Nessa epidemia 58% dos pacientes que tiveram amostras coletadas para análise tiveram o diagnóstico sorológico de ZIKV confirmado ou provável. Com os dados coletados dos acompanhantes de pacientes com suspeita de ZIKV, foi calculada uma taxa de infecção de 73% da população desta ilha (DUFFY et al., 2009).

Na Polinésia Francesa ocorreu em 2013 uma epidemia semelhante àquela ocorrida nas ilhas Yap. Dez por cento da população, perfazendo 8510 pacientes, foram consultados como casos suspeitos de ZIKV no período de 2013-2014. Amostras de 746 pessoas foram coletadas, e destas, 53% dos casos foram confirmados biologicamente (RT-PCR)(CAO-LORMEAU et al., 2014; IOOS et al., 2014).

Depois da epidemia na Polinésia Francesa, houve uma disseminação do vírus entre outras ilhas do pacífico e surtos de casos autóctones foram relatados na Nova Caledônia, Ilhas Cook (IOOS et al., 2014; MUSSO; CAO-LORMEAU; GUBLER, 2015; MUSSO; NILLES; CAO-LORMEAU, 2014). Em 2014, houve um surto de doença eritematosa na Ilha de Páscoa no Chile, onde 51 amostras de soro de pacientes tiveram RT-PCR positivo para o ZIKV. Nesta população, as cepas virais eram muito semelhantes às cepas do surto na Polinésia Francesa (TOGNARELLI et al., 2015). Esta foi a primeira aparição do ZIKV nas Américas.

No início do ano de 2015, o Brasil enfrentou um surto de uma doença exantemática inicialmente desconhecida, caracterizada por rash cutâneo, prurido, artralgias e edemas peri-articulares de curso limitado. Em março de 2015, Zanluca et. al, relataram a presença de ZIKV no soro de 8 indivíduos, no Rio Grande do Norte, com doença exantemática indeterminada, pela técnica de RT-PCR (ZANLUCA et al., 2015). Neste mesmo período, houve confirmação de casos de ZIKV por RT-PCR em 7 pacientes no estado da Bahia (CAMPOS; BANDEIRA; SARDI, 2015). Desde a sua entrada no Brasil, houve uma rápida disseminação do ZIKV, com registro de autoctonia desde abril de 2015 e um total aproximado de 440.000-1.300.000 casos até o mês de fevereiro de 2016 (PLOURDE; BLOCH, 2016). No ano de 2016 (semana epidemiológica 52), todos estados brasileiros e distrito federal tiveram registro de casos de infecção pelo ZIKV, com o total de 2.015.319 (taxa de incidência de 105,3 casos/100 mil hab.) (BRASIL, 2017).

Suspeitava-se que a chegada e a disseminação do vírus no Brasil teria sido facilitada pela Copa do Mundo de Futebol da FIFA em 2014 (SALVADOR; FUJITA, 2015). Apesar de os primeiros casos clínicos observados e a confirmação por métodos moleculares da doença exantemática relacionada ao ZIKV somente ocorrerem no final do ano de 2015, Faria et al. demonstraram que a introdução do vírus nas Américas parece ter ocorrido no período de maio a dezembro de 2013 através do método de relógio filogenético e molecular. A hipótese atual é de que a introdução do ZIKV ocorreu no Brasil no período da copa das confederações que ocorreu de 15 a 30 de junho de 2013 (FARIA et al., 2016).

No início do surto no Brasil, acreditava-se que o ZIKV era uma doença exantemática, autolimitada, sem manifestações graves, devido aos poucos relatos de comprometimentos graves em outras epidemias. Entretanto, diversos casos de complicações graves, tanto

neurológicas quanto não neurológicas foram descritas, principalmente a partir do surto na Polinésia Francesa em 2013. As complicações relacionadas ao ZIKV estão descritas na tabela 2 (BAUD et al., 2017).

Tabela 2. Complicações neurológicas e não neurológicas relacionadas a infecção por Zika vírus

Complicações neurológicas
Síndrome de Guillain-Barré
Encefalite
Mielite
Meningoencefalite
Polineuropatia sensitiva transitória/ Polineurite Transitória Aguda
Síndrome congênita relacionada ao ZIKV
Complicações oftalmológicas
Papiledema
Uveíte
Maculopatia
Complicações não neurológicas
Miocardite
Trombocitopenia severa
Mortes relacionadas ao ZIKV

Adaptado de: BAUD, D. et al. An update on Zika virus infection. The Lancet, v. 6736, n. 17, 2017.

A observação do aumento de casos de SGB foi observada primeiramente na epidemia da Polinésia Francesa em 2013, com a notificação de 72 casos neurológicos graves, e, destes, 40 casos de SGB, uma taxa 20 vezes maior que a esperada para aquele ano (IOOS et al., 2014). Apesar desta relação temporal entre o aumento de casos de ZIKV e aumento de SGB, apenas 1 caso teve confirmação sorológica (OEHLER et al., 2014). Um estudo de caso controle na população da Polinésia Francesa confirmou a associação entre a SGB e infecção por ZIKV. Neste estudo, a maioria dos indivíduos tinha infecção prévia por DENV, independentemente de estarem alocados no grupo caso ou controle, o que enfraquece a ideia de que indivíduos infectados primariamente por DENV em outras épocas possam ser mais susceptíveis a manifestações neurológicas quando infectados por ZIKV (CAO-LORMEAU et al., 2016). A correlação entre o aumento de casos de ZIKV e a consequente ascensão de manifestações de SGB podem ser visualizadas na Figura 1. No Brasil, essa associação entre aumento de casos de ZIKV e SGB também foi observada, principalmente na região nordeste e diversos casos já foram relatados na literatura (ARAUJO; FERREIRA; NASCIMENTO, 2016; DO ROSARIO et al., 2016; DOS SANTOS et al., 2016). O quadro clínico da SGB associada ao ZIKV é semelhante a outros casos de SGB por infecção por outros vírus, entretanto há a percepção de

ocorrência de maiores casos de variantes e acometimento de nervo facial. A ENMG no estudo caso-controle da Polinésia Francesa mostrou um padrão de polineuropatia axonal, enquanto que em outras populações a ocorrência típica é do padrão desmielinizante agudo (AIDP) (BAUD et al., 2017).

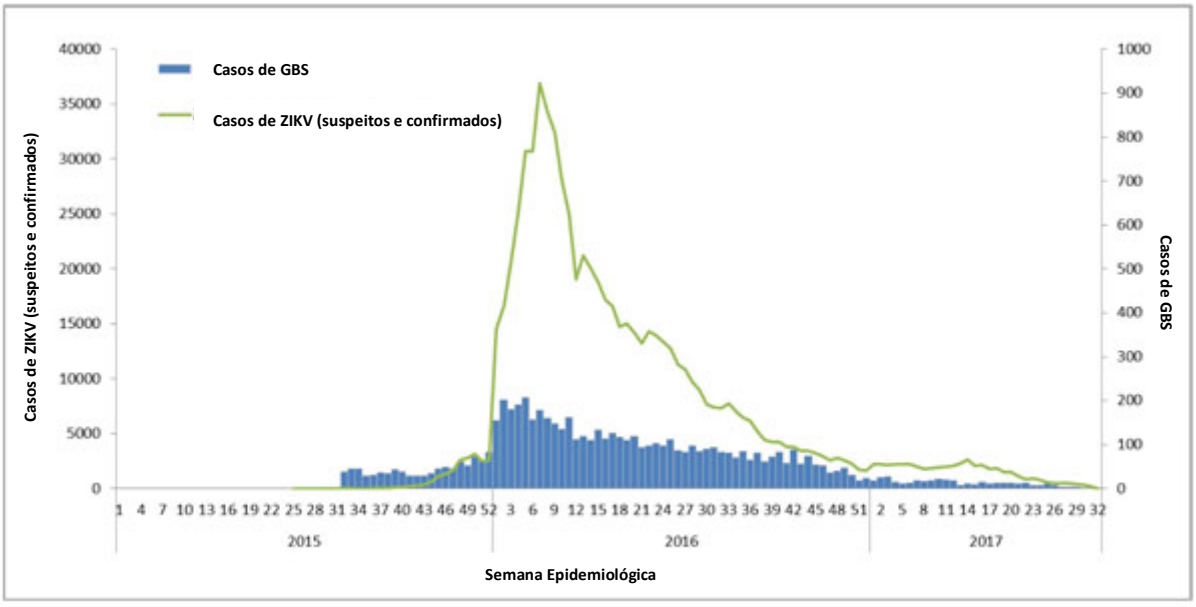

Figura 1: Distribuição dos casos de ZIKV e GBS entre 2015-2017 nas Américas
Fonte: PAHO/WHO. Website: http://www.paho.org/. Acessado em 05/09/2017.

Manifestações atípicas de neuropatia periférica foram observadas em alguns relatos de casos, classificados como polineurite transitória aguda (ATP)/polineuropatia sensitiva reversível (RSP). Tais manifestações eram mais leves, predominantemente sensitivas, sem alterações clássicas de SGB, como fraqueza em membros inferiores, arreflexia ou dissociação albuminocitológica. Foi observado no seguimento de 3 pacientes no Rio de Janeiro a presença dessas manifestações sensitivas, leves e sem alterações na ENMG, entretanto, em 2 deles, havia espessamento dos nervos sensitivos acometidos. Em outro relato de caso em Honduras, as mesmas manifestações ocorreram, entretanto, houve alteração no estudo de condução nervosa sensitiva na ENMG. Em todos esses casos as manifestações foram autolimitadas. A semelhança entre os quadros parece nos levar à percepção de que haja uma ação direta do vírus sobre os nervos periféricos sensitivos (DO ROSARIO et al., 2018; MEDINA et al., 2016; NASCIMENTO et al., 2017).

As manifestações em SNC são incomuns em infecção por ZIKV, entretanto 2 casos foram descritos: um caso de uma paciente brasileira com encefalite grave, evoluindo para óbito (SOARES et al., 2016) e outro paciente idoso que se infectou após um cruzeiro na Nova Zelândia e desenvolveu um caso de meningoencefalite com alterações em RNM de crânio, e se recuperou quase que completamente após 38 dias da admissão (CARTEAUX et al., 2016).

Outros casos de manifestações neurológicas foram relatados, como mielite em uma paciente de 15 anos de idade (MÉCHARLES et al., 2016), crise convulsiva isolada e hemiparesia e neuropatia craniana transitória em 2 pacientes com infecção aguda por ZIKV (ROZÉ et al., 2016), e alteração cognitiva crônica em um adolescente que viajara para as ilha do Caribe (ZUCKER et al., 2017).

2.5 COCIRCULAÇÃO E COINFECÇÃO

Devido à cocirculação de ZIKV, CHIKV e DENV, aumenta-se a preocupação sobre a ocorrência de coinfecção, principalmente pelo desconhecimento da gravidade das manifestações clínicas que esta apresentação concomitante pode acarretar. Alguns relatos de casos, principalmente na América Latina, já mostram essa situação, a maioria manifestando-se como síndromes febris agudas ou doenças exantemáticas agudas (CHERABUDDI et al., 2016; VILLAMIL-GÓ MEZ et al., 2016; VILLAMIL-GÓMEZ et al., 2016; WAGGONER et al., 2016). Entretanto, em uma série de 16 casos de pacientes com manifestações neurológicas, houve uma proporção de 75% de detecção de 2 ou 3 dos arbovírus CHIKV, DENV ou ZIKV. Nesta série, havia doenças como encefalites, mielites, SGB, meningites e vasculites encefálicas (ACEVEDO et al., 2017).

3. OBJETIVOS

OBJETIVO PRINCIPAL

1. Identificar e descrever as características clínicas, laboratoriais e eletrodiagnósticas de pacientes acometidos por diferentes síndromes neurológicas durante a tríade epidemia por arbovírus em unidades de referência em neurologia do estado da Bahia.

OBJETIVOS SECUNDÁRIOS

2. Descrever as manifestações clínicas, laboratoriais e eletrodiagnósticas dos casos de SGB e suas variantes.
3. Avaliar a possível associação entre SGB e suas variantes com infecção por CHIKV, DENV ou ZIKV através de estudos sorológicos ou técnicas moleculares (RT-PCRq).
4. Descrever a evolução dos pacientes com SGB e suas variantes reavaliados 30 dias após a alta hospitalar.
5. Descrever as características clínicas dos pacientes diagnosticados com a forma neurológica mais leve (PTA/PST) e correlacionar com achados de sorologias para ZIKV, CHIKV e DENV.
6. Descrever as características clínicas de uma paciente com síndrome rara (SOMA) e sua confirmação com detecção de CHIV e DENV por técnicas moleculares (RT-PCRq).

4. ARTIGO 1 - Case Report: Guillain–Barré Syndrome after Zika Virus Infection in Brazil

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Fator de impacto: 2,564

Artigo escrito no início do surto da tríade arboviral em 2015. Uma das primeiras descrições de síndrome de Guillain-Barré ocorrida após a infecção pelo vírus zika em Salvador, Bahia, Brasil.

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Case Report: Guillain–Barré Syndrome after Zika Virus Infection in Brazil

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Abstract. Zika virus (ZIKV) is an emerging flavivirus, which has caused a widespread outbreak in the Americas. Shortly after its introduction in 2015, a cluster of cases with Guillain–Barré syndrome was detected in Brazil. Herein, we describe two cases from the city of Salvador, who developed ascending paresis after an acute exanthematous illness. The patients were admitted to the intensive care unit with tetraparesis and cranial nerve palsy, which resolved after intravenous administration of human immunoglobulin. Serological evaluation detected IgM-specific ZIKV antibodies. In regions of Zika virus transmission, health-care workers must be aware of the potential severe neurological complications associated with ZIKV infection and be prepared to provide prompt diagnosis, treatment, and supportive care.

INTRODUCTION

Zika virus (ZIKV) is an emergent flavivirus transmitted by *Aedes aegypti* mosquitoes with a high potential for transmission in countries where infestation of the vector occurs.[1] The first documented human case of ZIKV infection was reported in Nigeria in 1954,[2] and a number of sporadic cases were reported in Africa and Asia in subsequent years.[3] ZIKV was first associated with a large outbreak beginning in 2007 in Micronesia,[4] and later at French Polynesia in 2013,[5,6] and New Caledonia in 2014.[7] ZIKV was initially detected in northeastern Brazil on March 2015,[8,9] and has rapidly spread throughout South and Central America and the Caribbean.[10]

Human ZIKV infection was considered as a benign and self-limited illness, with clinical manifestations represented by low-grade fever, maculopapular rash, myalgia, arthralgia, headache, and conjunctivitis.[4] However, neurological complications were observed in patients during a ZIKV outbreak in French Polynesia in 2013, where several individuals presented with Guillain–Barré Syndrome (GBS).[5] A subsequent investigation found evidence of association between GBS and ZIKV infection.[11]

Similarly, after detection of ZIKV transmission in Brazil,[8] a cluster of GBS cases was identified.[10] Herein, we describe two patients presenting with GBS associated with ZIKV infection during the outbreak in Salvador, situated in the northeast region of Brazil. These patients presented severe complications of GBS requiring admission to the intensive care unit.

CASE REPORT

Patient 1. A 49-year-old female presented with transient symptoms of generalized pruritic maculopapular rash and myalgia without fever or arthralgia, which lasted one day on May 15, 2015 (Day −10). On May 25 (Day 0: onset of neurological symptoms), she presented paresthesia on both hands and feet. Four days later, she noticed generalized fatigue and lower right limb paresis, followed by upper limb paresis. On Day 9, she developed diplopia and dysphagia appeared, and presented to an emergency room by Day 11, when she developed bilateral facial nerve palsy. She was hospitalized on Day 20 with worsening extremity weakness and ataxia.

She had weakness of her four limbs (Medical Research Council, MRC grade 4), areflexia, impairment of all sensitivity modalities and moderate bifacial nerve palsy (House–Brackmann grade 3). A lumbar puncture yielded cerebrospinal fluid (CSF) with 10 cells/mm^3, with a predominance of lymphocytes, and protein and glucose level of 214 and 70 mg/dL, respectively. Diagnosis of GBS with tetraparesis and bifacial palsy was established according to international criteria,[12] and treatment was initiated on Day 23 with 0.4 g/kg/day of intravenous human immunoglobulin (IVIG) for 5 days. The patient's clinical and laboratory data are summarized in Table 1. Rapid clinical response was observed with improvement of muscular strength and bifacial palsy (House–Brackmann grade 2) by Day 26. Hughes functional grade was used to access the improvement of disability.[13] This patient improved from grade 4 to grade 2 by day 28.

On Day 58, during outpatient visit, she was able to walk unaided, had normal strength, sensitivity, and reflexes, and a mild residual bifacial palsy (House–Brackmann grade 2) on physical examination. The electromyogram, performed on Day 75, confirmed multifocal segmental demyelinating commitment with prolonged distal latencies and F-waves, with no reduction of compound motor action potential (CMAP). Reduction of sensory action potential amplitudes of median and ulnar nerves suggested secondary axonal injury (Table 1).

Patient 2. A 22-year-old male presented with fever, maculopapular generalized rash, and moderate arthralgia on May 30, 2015 (Day −8), which persisted for 5 days. These symptoms resolved and 3 days later (Day 0: onset of neurological symptoms), he had paresthesia on both feet and hands. On Day 3, he was tetraparetic and developed right-sided peripheral facial nerve palsy, dysarthria, urinary and fecal incontinence, and a transient blurred vision. On Day 4, he developed bifacial palsy and dysphagia, and he was admitted.

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TABLE 1
Clinical and laboratory characteristics of two patients with Guillain–Barré syndrome from Salvador, Brazil

Characteristics	Case 1	Case 2
Age	49	22
Sex	Female	Male
Acute prodrome (duration)	Myalgia, rash, pruritus (1 day)	Fever, arthralgia, rash, pruritus (5 days)
Onset of neurological symptoms after prodrome	10 days	8 days
Neurological findings	Tetraparesis, bifacial palsy, ataxia, paresthesias, and other sensory distrubances	Tetraparesis, bifacial palsy, paresthesias, and other sensory distrubances
Cerebrospinal fluid findings	10 cells/mm^3; protein, 214 mg/dL; glucose, 70 mg/dL	5 cells/mm^3; protein, 67 mg/dL; glucose, 53 mg/dL
Electromyogram and nerve conduction study findings	Ulnar nerve: DL = 6.2 ms (RV < 3.0); CMAP = 7.4 mV (> 8.0 mV); NVC elbow = 52.1 m/s (> 50 m/s); F-wave: 32.6 ms (< 27 ms)	Ulnar nerve: DL = 3.4 ms (RV < 3 ms); CMAP = 13.9 mV (> 8.0 mV); NVC elbow = 30.3 m/s (> 50 m/s); F-wave = 40.2 ms (< 29 ms)
	Tibialis nerve: DL = 7.7 ms (< 5.0 ms); CMAP = 7.7 mV; NVC = 4.4 m/s	Median nerve: DL = 7.5 ms (< 3.7 ms); CMAP = 11.1 mV (> 8 mV); NVC = 54.2 m/s (> 50 m/s)
	Facial nerve: DL = 9.6 ms (< 3.0 ms); CMAP = 0.2 mV (> 1.5 mV)	Tibialis nerve: DL = 47 ms (< 5.0 ms); CMAP = 15.2 mV (> 4.0 mV); NVC = 49.7 m/s (> 40 m/s);
		Facial nerve: DL = 4.0 ms (< 3.0 ms); CMAP = 1.1 mV (> 1.5 mV); R1 = 20.0 ms/R2 = 47.8 ms (< 10.0/< 30.0 ms);
Treatment (duration)	Intravenous human gamma globulin (5 days)	Intravenous human gamma globulin (5 days)
Days of hospitalization	9	24

CMAP = conduction motor action potential; DL = distal latency; NVC = nerve conduction velocity; RV = reference value.

He became bedridden due to severe tetraparesis on Day 7 (MRC grade 2, upper limbs; grade 3, lower limbs) and was transferred to the neurological intensive care unit. He was alert, there was areflexia in all extremities, severe sensory impairment on all modalities, and moderately severe bifacial palsy (House–Brackmann grade 6). A nasoenteric tube was inserted because of severe dysphagia. Examination of CSF revealed 5 cells/mm^3 with a predominance of lymphocytes and levels of protein and glucose of 67 and 53 mg/dL, respectively. The patient's clinical and laboratory findings are summarized in Table 1.

A diagnosis of GBS with bifacial palsy, tetraparesis, and brainstem involvement was established, and treatment with 0.4/kg/day of human IVIG for 5 days was initiated on Day 8. He recovered over the following 20 days with gradual improvement of muscular strength, dysphagia, dysphonia, and ability to walk with unilateral assistance. He improved from Hughes functional grade 4 to 3, and was discharged on Day 28. Electromyogram performed on Day 31 showed bilateral demyelinating impairment of median and ulnar nerves at wrist and ulnar nerve impairment at elbow, with prolonged distal motor latencies, reduced sensory conduction velocities in distal segments, and reduced motor conduction velocities of ulnar nerves with prolonged latencies of the F-waves and normal amplitudes of CMAP. Proximal demyelinating commitment of right facial nerve, with increase in blink reflex latencies (R1 = 20 ms/R2 = 55 ms), and mild reduction in the amplitude of CMAP was also noted (Table 1).

On Day 47, the patient did not have sensitivity or muscular strength abnormalities but had a mild/moderate right facial palsy (House–Brackmann grade 3) and areflexia in upper and lower limbs.

Laboratory evaluation. Serological tests for human immunodeficiency virus, hepatitis B and C were negative in both cases, as well as an IgM enzyme-linked immunosorbent assay (ELISA) for cytomegalovirus and herpes simplex virus type 1 and 2. Reverse transcription polymerase chain reaction (RT-PCR) for ZIKV, chikungunya virus (CHIKV), and

TABLE 2
Serological evaluation of two patients with Guillain–Barré syndrome from Salvador, Brazil

Test	Case 1	Case 2
IgM ELISA*		
ZIKV	**0.765**	**1.357**
CHIKV	0.092	0.093
DENV	0.062	0.181
YFV	0.041	0.094
HI (IgG + IgM)		
ZIKV	≥ 1:1,280	≥ 1:1,280
CHIKV	Negative	Negative
DENV-1	1:320	≥ 1:1,280
DENV-2	1:640	≥ 1:1,280
DENV-3	1:320	≥ 1:1,280
DENV-4	1:640	≥ 1:1,280
YFV	1:160	≥ 1:1,280
$PRNT_{90}$		
ZIKV	320	> 2,560
CHIKV	< 20	< 20
DENV-1	> 640	ND
DENV-2	320	> 2,560
DENV-3	160	1,280
DENV-4	80	160
YFV	< 20	< 20

CHIKV = chikungunya virus; DENV = dengue virus; ELISA = enzyme-linked immunosorbent assay; HI = hemagglutination inhibition; ND = not determined; $PRNT_{90}$ = plaque reduction neutralization test with a 90% neutralization cutoff; YFV = yellow fever virus; ZIKV = Zika virus. Positive values are in bold.
*Optical densities, cutoff = 0.200.

dengue viruses (DENV) were negative on blood samples collected on Day 23 for case 1 and on Day 8 for case 2.

Specific anti-ZIKV IgM antibodies were detected in patients 1 and 2 when acute-phase serum samples collected on Days 23 and 8 respectively, before administration of IVIG, were tested in an in-house IgM antibody capture ELISA(MAC-ELISA) (Table 2). Evaluation of these samples in CHIKV, DENV, yellow fever virus (YFV), and Mayaro virus MAC ELISA yielded negative results. A hemagglutination inhibition (HI) assay performed using a panel of 18 arboviruses, which included alphaviruses, orthobunyaviruses, and flaviviruses, demonstrated prior exposure to flavivirus infection (ZIKV and DENV1–4). These findings were confirmed by testing serum samples from the patient in a plaque reduction neutralization test (PRNT) against ZIKV, CHIKV, YFV, and DENV (serotypes 1–4) (Table 2). Taken together, the serological findings of both patients indicated a recent infection by ZIKV and argued for resolute infections by DENV1–4.

DISCUSSION

ZIKV is a reemerging pathogen, which poses new and unforeseen challenges for regions with recent outbreaks, representing an important threat for Latin America and other regions at risk.[14] Aside from the expected burden of an acute febrile illness to the health-care systems in the regions affected, the identification of potential causality between ZIKV and neurological complications results in an urgent concern with dramatic consequences to public health.

The term GBS is used to describe a broad spectrum of acute autoimmune neuropathies.[12] About two-thirds of the patients report an antecedent acute infectious illness and numerous infectious agents are associated with GBS.[12] An association with arboviruses, such as DENV[15] and CHIKV,[16] have been reported but are believed to be rare events. GBS cases were associated with ZIKV infection during the French Polynesia outbreak in 2013.[11]

This report describes two cases that were identified during a large outbreak in the city of Salvador, Brazil, in 2015, where 17,440 cases of suspected ZIKV infection were reported.[17] Concomitantly, 44 GBS cases, were identified, of which 32 (73%) reported having an acute prodromal illness, compatible with ZIKV infection.[17] Our patients had acute prodromal illness of pruritic rash, fever, mylagias, or arthralgias, which occurred 8–10 days before the onset of the neurological manifestations of GBS. Diagnosis of recent ZIKV infection was made based on detection of anti-ZIKV–specific IgM antibodies. Of note, like the GBS cases from French Polynesia,[11] RT-PCR analysis of serum samples at the time of the onset of neurological manifestations yielded negative results, indicating, presumably, the development of an anti-ZIKV immune response.

Underlying factors that influence the association of GBS and a recent ZIKV infection presumably involves an autoimmune process as described for other viral infections.[12] It has been speculated that the simultaneous epidemics of DENV and ZIKV may be a predisposing factor for GBS after a recent ZIKV infection, perhaps as a result of sequential arboviral immune stimulation and triggering of an immunopathogenic process.[11,18] We found that the two GBS cases, who are residents of a region of high DENV-endemic transmission,[19] had high HI and $PRNT_{90}$ (PRNT with a 90% neutralization cutoff) to DENV serotypes, indicating that the patients had a distant infection with this virus, before their recent ZIKV infection. However, in a case-control study at French Polynesia, the authors could not find evidence of an association between previous dengue infection and development of GBS.[11] They also observed the absence of typical patterns of antiglycolipid antibodies and suggested that onset of GBS may be attributed to unidentified autoantibodies in post-Zika virus exposure.[11] Thus, further immunopathologic studies are still required for better understanding of this issue.

Both patients had clinical and laboratory findings of GBS, with albuminocytologic dissociation. Electromyogram pattern showed distal demyelinating disorder with accentuated prolonged distal latencies and minimal reduction of CMAP amplitudes, suggesting an acute inflammatory demyelinating polyneuropathy (AIDP) GBS subtype,[20] with secondary axonal injury. The patients received and tolerated human IVIG treatment with no relevant adverse effects. The better prognostic of AIDP GBS subtype[20] along with prompt implementation of human IVIG treatment may have had an important role in clinical recovery. As illustrated, patients with severe GBS require intensive supportive management in intensive care settings. Yet, despite the severity of their clinical presentations, none of them needed mechanical ventilation or died.

The investigation of these two cases provides additional evidence in support of the association of GBS and ZIKV infection. Furthermore, it also serves as an alert to clinicians in regions of South and Central America and the Caribbean, where the virus has recently spread, of the potential risk for GBS and the need for timely detection, diagnosis, and initiation of treatment and supportive care to prevent mortality and long-term sequelae.

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5. ARTIGO 2 Opsoclonus-Myoclonus-Ataxia Syndrome associated with Chikungunya and Dengue Virus coinfection

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Case Report

Opsoclonus-myoclonus-ataxia syndrome associated with chikungunya and dengue virus co-infection

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ABSTRACT

Opsoclonus-myoclonus-ataxia syndrome (OMAS) is a rare neurological disorder characterized by irregular multidirectional eye movements, myoclonus, cerebellar ataxia, sleep disturbances, and cognitive dysfunction. Although most commonly related to paraneoplastic syndrome, this condition has occasionally been described following infectious illnesses. This article reports the first case of OMAS in association with chikungunya and dengue virus co-infection. The genetic analysis identified chikungunya virus of East/Central/South African genotype and dengue serotype 4 virus of genotype II. This report represents an unusual clinical syndrome associated with viral co-infection and reinforces the need for clinical vigilance with regard to neurological syndromes in the context of emergent arboviruses.

Introduction

Opsoclonus-myoclonus-ataxia syndrome (OMAS), or dancing eyes syndrome, is a rare neurological disorder characterized by irregular multidirectional eye movements, myoclonus, and, less frequently, cerebellar ataxia, sleep disturbances, and cognitive dysfunction (Gorman, 2010). OMAS, first described in 1962, has classically been related to neuroblastoma in children as a paraneoplastic syndrome. Post-infectious OMAS, with benign recovery, has occasionally been described, including virus-associated OMAS following infection caused by dengue virus (DENV) (Tan et al., 2014) and other viruses (Gorman, 2010).

Co-infection with DENV and chikungunya virus (CHIKV) was first reported in 1962 in Thailand (Nimmannitya et al., 1969). Other studies later reported patients co-infected with CHIKV and DENV, in which the co-infection mostly resulted in an acute febrile syndrome with non-specific features (Furuya-Kanamori et al., 2016).

This article reports a case of encephalitis and OMAS associated with DENV–CHIKV co-infection, which occurred in June 2015 during the peak of a concurrent arbovirus outbreak in Salvador, the capital of the state of Bahia, located in northeastern Brazil.

Case report

In June 2015, a 38-year-old black woman reported generalized pruritus, skin rash, and arthralgia. Although these symptoms remitted 5 days later, her family members noted abnormal head movement and chaotic eye movement. These symptoms worsened, accompanied by confusion, dysarthria, dysphagia, and hypersomnolence. Eight days later, she was admitted to a neurological intensive care unit, at which time she was confused, lethargic, and uncooperative. The patient's orientation, language, calculation, praxis, gnosis, and memory were difficult to assess as she could not speak clearly due to confusion. She could not obey simple commands such as open and close the eyes or squeeze hands. The neurologist noted rapid, involuntary, multivectorial,

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unpredictable, conjugate rapid eye movements in the absence of intersaccadic intervals, characteristic of opsoclonus (**Supplementary material**, Video). Mild ataxia during the index–nose–finger test was noted bilaterally. There were no signs of meningismus.

Computed tomography (CT) of the cranium and contrast-enhanced magnetic resonance imaging (MRI) with thin cuts of the brainstem (FIESTA sequence) were normal. Cerebrospinal fluid (CSF) examination showed a white blood cell count of 3×10^6 cells/l (with lymphocyte predominance), glucose level of 111 mg/dl, and protein level of 33 mg/dl. GQ1b autoantibody tests were negative. Chest and abdomen CT, as well as gynecological and manual breast examinations were performed as standard cancer screening for the patient's age; all of these examinations were unremarkable.

Three days after admission, a course of human intravenous immunoglobulin (IVIG) was administered at 2 g/kg (total dose) for 5 days. She exhibited a mild improvement and 4 days later, a 5-day course of methylprednisolone pulse therapy (1 g/day) was started. No antibiotics or antiviral agents were given. One week after pulse therapy, she demonstrated further improvement: the opsoclonus symptoms had become milder and she was lucid and speaking clearly. Three weeks later, the patient exhibited normal cognitive function with no signs of ataxia or opsoclonus and was discharged.

One month after discharge the patient attended an outpatient appointment. She continued to have no signs of opsoclonus, ataxia, or cognitive impairment. Written informed consent was obtained from this patient to participate in the present case study.

Methods

Plasma, serum, and CSF were collected on admission, 8 days after the onset of viral symptoms. The detection of specific IgM antibodies for CHIKV and DENV was performed with CHIKV IgM ELISA (Euroimmun, Lübeck, Germany) and NovaLisa Dengue IgM ELISA (NovaTec Immundiagnostica GmbH, Dietzenbach, Germany), respectively, according to the manufacturer's recommendations.

Serological testing for HIV and hepatitis B and C viruses (HBV, HCV) was also performed, in addition to testing for cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1/2), and Zika virus (ZIKV) (NovaLisa ZIKV IgM μ-capture ELISA; NovaTec Immundiagnostica GmbH, Dietzenbach, Germany).

Reverse transcription real-time PCR (RT-qPCR) was performed for CHIKV, DENV, and ZIKV, as described previously (Johnson et al., 2005; Chiam et al., 2013). Partial viral genomes were recovered and nucleotide sequences were subtyped using the arbovirus subtyping tool (http://bioafrica2.mrc.ac.za/rega-genotype/typingtool/aedesviruses/). Phylogenetic reconstructions were performed using CHIKV and DENV reference strains obtained from the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). The datasets consisted of the novel CHIKV and DENV sequences obtained herein, in addition to publicly available complete genome sequences (CHIKV West African, East/Central/South African (ECSA), Indian Ocean Lineage (IOL), and Asian genotypes; DENV serotypes 1–4, genotypes I–III and sylvatic). Maximum likelihood phylogenetic trees were generated as described previously (Giovanetti et al., 2016).

Results

IgM ELISA yielded negative results for CHIKV, but was positive for DENV in the sample collected on admission. Serological testing was also negative for ZIKV IgM, CMV IgM, HSV-1/2 IgM, HIV, HBV, and HCV.

RT-qPCR for CHIKV was positive for plasma and CSF samples collected on admission. RT-qPCR for DENV was also positive for the same plasma sample, while RT-qPCR for ZIKV was negative for both samples. Partial genome sequences were recovered for two different regions of CHIKV, one at gene E2 (1885 nt; position 120–2008) and another at gene E1 (997nt; position 7639–8635), corresponding to 26% of the entire genome. Several regions of DENV were recovered, ranging from 160 nt to 1480 nt in length, covering approximately 64% of the entire genome.

Figure 1. (A) Maximum likelihood tree, mid-point rooted, including the isolate of CHIKV from Brazil, in addition to 75 reference sequences. The GenBank accession number, year of isolation, and country of origin are indicated on the tips of the tree for all strains except for the newly obtained CHIKV isolate from Salvador, Bahia, Brazil (**KY421925**), which is highlighted in bold. (B) Maximum likelihood tree, mid-point rooted, including the newly isolated sequence of DENV from Brazil, in addition to 40 reference sequences. The GenBank accession number, year of isolation, and country of origin are indicated on the tips of the tree for all strains except for the newly obtained DENV isolate from Salvador, Bahia, Brazil (**KY421926**), which is highlighted in bold. The scale is expressed in units of nucleotide substitutions per site. Asterisks represent bootstrap values >90%.

The CHIKV maximum likelihood phylogenetic reconstruction indicated that the isolate belonged to the ECSA genotype. The DENV maximum likelihood reconstruction further indicated that the DENV genome belonged to serotype 4 DENV (DENV-4) of genotype II, with bootstrap support >90% (Figure 1). These new CHIKV and DENV-4 sequences have been deposited in the GenBank database under accession numbers **KY421925** and **KY421926**, respectively.

Discussion

Emergent and re-emerging arboviruses pose new and unforeseen challenges in regions affected by recent outbreaks. The identification of neurological complications arising from arboviruses has raised new public health concerns, mainly related to Guillain–Barré syndrome in association with ZIKV (do Rosario et al., 2016). Neurological complications associated with DENV or CHIKV are believed to be unusual. Relatively few cases of dengue-associated encephalitis have been reported; however reports of CHIKV-associated encephalitis increased during the 2005–2006 CHIKV outbreak on the island of La Réunion (Bintner et al., 2015).

The current medical literature contains few reports of arbovirus-associated OMAS. It appears that this is the first case report to describe OMAS related to CHKV–DENV infection. In fact, no cases of OMAS in association with CHKV have been reported to date, and a literature review identified just four cases of DENV-associated OMAS (Tan et al., 2014; Verma et al., 2014).

Empirical therapy for OMAS consists of immunosuppressive agents. Meanwhile, OMAS associated with viral infection seems to have a benign outcome, with prompt recovery observed in response to corticosteroids, or even full recovery without specific therapy (Gorman, 2010). While the case reported herein was initially treated with IVIG, resulting in a mild improvement, full recovery was only obtained after a course of methylprednisolone pulse therapy. Previously reported dengue-related OMAS cases were treated with low-dose clonazepam or prednisolone, with complete recovery occurring similarly to the present case (Tan et al., 2014).

While the pathogenesis of OMAS is not completely understood, autoimmune-mediated dysfunction has been suggested as the underlying mechanism (Blaes et al., 2008). It has been hypothesized that sequential arbovirus infections may cause immunological enhancement, which could be related to severe clinical forms of dengue (Solomon et al., 2000), or the triggering of neurological complications in ZIKV infection (Cao-Lormeau et al., 2016). Accordingly, it is possible that the co-infection by two distinct arboviruses seen in this case may have brought about the onset of OMAS.

Due to the similarity in transmission vector and geographical distribution of outbreaks, CHIKV–DENV co-infection could plausibly arise in endemic regions. However, as a result of similarity in clinical presentation, co-infection could well go undiagnosed. Many cases described previously as co-infections utilized serology as a diagnostic technique, which does not rule out the possibility of sequential infection, as opposed to concomitant infection. In the case presented here, CHIKV–DENV co-infection was diagnosed based on the RT-qPCR detection of both viruses in a single plasma sample, thereby confirming the concomitant nature of the reported co-infection. Furthermore, the presence of CHIKV RNA in the patient's CSF sample highlights the potential of this emergent arbovirus to present possible neurotropism.

Phylogenetic analysis indicated that this patient was co-infected with CHIKV ECSA and DENV-4 genotype II. The CHIKV ECSA genotype was introduced into Bahia, Brazil in mid-2014 (Nunes et al., 2015), and since the first detection of DENV-4 in Brazil in 1982, phylogeographic analyses have confirmed the co-circulation of two distinct DENV-4 genotypes (I and II) in Brazil (Nunes et al., 2012).

In summary, this report describes a case presenting CHIKV–DENV co-infection in association with OMAS, which reinforces the potential association between emergent arboviruses and neurological syndromes. This case should serve as an alert for clinicians to be vigilant with respect to neurological complications in regions affected by arbovirus outbreaks.

Author contributions

(1) Research project: A. conception; B. organization, C. execution; (2) Statistical analysis: A. design, B. execution, C. review and critique; (3) Manuscript: A. writing of the first draft, B. review and critique. MSR: 1A, 1B, 1C, 3A, 3B; MG: 2A, 2B, 3B; PAPJ: 1B, 1C, 3B; DSF: 1B, 1C; NRF: 2A, 2B, 2C, 3B; CPSL: 1B, 1C; SPS: 1B, 1C; MRN: 1B, 1C, 3B; LCJA: 1A, 2A, 2C, 3B; ICS: 1A, 1B, 2A, 3A, 3B.

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Ethical approval

Written informed consent was obtained from this patient for participation in the present case study.

Conflict of interest

The authors deny the existence of any potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.07.019.

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6. ARTIGO 3: Reversible sensory polyneuropathy during an arboviral outbreak in Salvador, Bahia, Brazil

Situação do artigo: Publicado
Revista: Journal of the Neurological Sciences
Tipo: Clinical/Scientific Notes (letter to the editor)
Fator de Impacto: 2,295
Ano: 2018

Descrição de cinco casos de pacientes com alteração neurológica limitada à sensibilidade, de curso benigno e reversível. Poucos casos foram descritos na literatura e houve a ocorrência da associação desta entidade com o vírus chikungunya pela primeira vez nessa descrição atual.

Journal of the Neurological Sciences 391 (2018) 3–4

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Letter to the Editor

Reversible sensory polyneuropathy during an arboviral outbreak in Salvador, Bahia, Brazil

ARTICLE INFO

Keywords:
Reversible sensory polyneuropathy
Zika virus
Chikungunya virus

Dear Editor,

Guillain-Barré syndrome (GBS), an acute, immune- mediated polyradiculoneuropathy, typically occurs in response to minor viral and bacterial infections. Associations between this syndrome and previous arboviral infection, such as dengue (DENV), chikungunya (CHIKV) or Zika virus (ZIKV), have been reported in some studies [1,2]. GBS usually manifests as generalized weakness and areflexia, accompanied by sensory and autonomic disturbances [3]. Mild neurologic syndromes associated with ZIKV infection have previously been described, characterized by short-term isolated sensory disturbances [4,5]. Here we describe five cases of reversible sensory polyneuropathy occurring during the 2015 arboviral outbreak in Salvador, Bahia-Brazil.

This article describes a case series of five patients admitted to two tertiary hospitals located in the city of Salvador during the 2015 outbreak of ZIKV, CHIKV and DENV in Brazil. This study was approved by the institutional review board of Fundação Oswaldo Cruz – Bahia (1184454/2015). All patients were provided a written term of consent prior to participation in this study.

Blood and cerebrospinal fluid (CSF) was collected upon admission and serological testing for arboviruses was performed to detect anti-DENV and anti-CHIKV IgG and IgM antibodies, as well as anti-ZIKV IgG antibodies, by enzyme immunoassay (ELISA) using the Euroimmun® commercial kit. Anti-Zika IgM antibodies were detected by an in-house capture ELISA (CDC-Atlanta) [6]. Serum samples were also tested in a plaque reduction neutralization test (PRNT) against ZIKV and CHIKV. Moreover, according to the recommendations of the Brazilian Ministry of Health and due to the time of sample collection (> 5 days between onset of symptoms and collection of the samples), the molecular diagnosis by PCR was not performed. [7]

Additional blood tests were conducted to rule out any alternative causes of muscular/peripheral nerve disorders. Electrophysiology studies (EMG and nerve conduction studies) were performed in two patients by a certified neurologist with specialized training in neuromuscular diseases. All examinations included nerve testing in both the upper and lower extremities and F-wave testing.

Five patients presented with predominant sensory symptoms: stocking-glove paresthesia (100%) and hypoesthesia (75%). No abnormalities in gait, cranial nerves or reflexes were noted. The Hughes functional scale (HFS) (grades: 0–6) was used to evaluate disease severity, with the highest values corresponding to the greatest degree of neurological dysfunction [8]. The neurological manifestations in these patients were considered mild (100% had HFS < 2) and only one required hospitalization. All of them reported previous acute viral symptoms. The mean duration of symptoms was 7.0 days ($\pm$ 3.08), and the mean difference between the onset of virus symptoms and neurological manifestation was 15.4 days ($\pm$ 10.31). EMG detected no abnormalities in the two patients tested. The mean CSF protein value was 26 mg/dL (RV $<$ 40 mg/dL). Muscle enzyme, inflammatory, serology testing (HIV, HTLV, CMV, EBV, HCV, HBV, syphilis) and other routine laboratory results were unremarkable.

Two patients tested positive for anti-CHIKV IgM antibodies. Another two patients exhibited positivity for anti-ZIKV antibodies (one IgG alone and the other IgM and IgG). Anti-DENV IgG antibodies were present in all patient's sera. No patients presented positivity for DENV IgM antibodies. PRNT assays indicated exposure to CHIKV in two subjects, whereas the serological findings for ZIKV exposure indicated a recent infection for two subjects, confirming the results obtained in ELISAs tests.

Several cases of GBS and other neurological syndrome related do ZIKV and CHIKV had already been reported [9,10]. However, isolated cases of a neurological syndrome characterized by a milder presentation than GBS, which did not meet GBS criteria due to a lack of clinical, ENM or CSF abnormalities, were previously described in association with ZIKV infection, termed as acute transient polyneuritis (ATP) or reversible sensory polyneuropathy (RSP) [4,5]. Here we report five patients with reversible sensory polyneuropathy, characterized as mild disease (HFS $<$ 2), presenting with exclusive sensory disturbance and no alterations in CSF or EMG studies. Serology results demonstrated that all patients (100%) presented evidence of previous arboviral infection, while most patients (80%) demonstrated recent infection by ZIKV or CHIKV. Peripheral neuropathy related to CHIKV had already been described in previous reports [11], however, to best of our knowledge, this is the first report of two cases describing this specific subtype of peripheral neuropathy (RSP) with strong evidence of recent CHIKV infection. Association with ZIKV was previously reported in case series with similar clinical findings, hypothesizing that these may have been a direct neuropathic or inflammatory effect of ZIKV, characterized by reversible inflammation and sensory nerve swelling [4,5], and recently it was hypothesized that ZIKV could direct infect peripheral neurons and promote cell death [12]. This report should serve as an important reminder to physicians and health care professionals to be alert in identifying other forms of neurological diseases possibly related to ZIKV and CHIKV infection.

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7. ARTIGO 4: Guillain-Barré syndrome and its subtypes during an arboviral outbreak in Salvador/Bahia

Situação do artigo: Submetido

Revista: Brain

Tipo: Brief Report

Fator de Impacto: 10,292

Ano: 2018

Descrição de série de casos de síndrome de Guillain-Barré e suas variantes com dados clínicos, laboratoriais (sorologias) e eletroneuromiográficos e evoluçõ clínica.

Guillain-Barré syndrome and its subtypes during an arboviral outbreak in Salvador/Bahia

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SUMMARY

Guillain-Barré syndrome (GBS) associated with arbovirus such as zika, chikungunya and dengue were previously reported. Methods: Case series of patients followed during zika outbreak in Salvador in 2015-2016. Blood, serum and CSF samples were collected for virus identification. Serologic studies for the 3 arboviruses was performed. EMG was also performed. Results: Fourteen patients were accompanied, and half of the cases were GBS variants. Zika was present in 78% and chikungunya in 14% of the patients. EMG pattern was AIDP. Discussion: Most patients had evidence of zika, but some had chikungunya evidence of previous infection also. There was a high incidence of GBS subtypes.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy typically occurring 2–8 weeks after viral or bacterial infections. Motor function is usually affected, beginning distally and progressing proximally over up to a 4-week period. Areflexia, sensory disturbances and cranial nerves involvement can also occur. There are diverse clinical subtypes with different neurological features, such as MFS, Bickerstaff syndrome and other variants 1.

About two thirds of the patients with GBS report an antecedent acute infectious illness and numerous infectious agents are associated with GBS, usually Campylobacter jejuni, Cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and Mycoplasma pneumoniae 2,3. GBS triggered by arboviruses, such as DENV, CHIKV and ZIKV, have been reported in some studies4,5.

Zika virus (ZIKV) is a flavivirus transmitted by Aedes aegypti mosquitoes6. The first documented human case of ZIKV infection was reported in Nigeria in 1954 7, with a number of sporadic cases reported in Africa and Asia in subsequent years 8. More recently, ZIKV re-emerged, causing several outbreaks in Pacific Ocean countries 9 and then detected in Northeastern Brazil in 2015 10,11 and rapidly spreading throughout South and Central America and the Caribbean 12. Chikungunya virus (CHIKV), was first described in Africa in 1952. Restricted epidemics occurred limited to Asia and Africa until global epidemics at Reunion Island in 2005 and French Polynesia in 2013 occurred 13. CHIKV was reported in Brazil in 2014 and its rapidly disseminated throughout the country14. DENV circulates in Brazil since 1845 and is one of the main diseases with public health impact in this country. It is transmitted to humans through inoculation by mosquitoes of the genus Aedes. Since 1981 various outbreaks occurred in Brazil and since 2010 there is cocirculation of 4 serotypes (DEN1 - DEN4) 15.

The observation of the increase in GBS cases possibly associated with ZIKV was first observed in the French Polynesia (FP) epidemic in 2013 with the notification of 72 severe neurological cases and 40 cases of GBS, a rate 20 times higher than expected year 16. A case control study in FP population confirmed the association between GBS and ZIKV infection 17. In Brazil, the association between increased cases of ZIKV and GBS was also observed, mainly in the northeast region and several cases have been reported in the literature 18,19. During an outbreak of CHIKV in FP in 2014 an increase in GBS cases were also described. The association of GBS and DENV infection is rare and is usually described in case reports 20.

Due to a probable correlation between GBS and arboviral disease, we proposed a case series study in two hospitals in Salvador, Bahia, Brazil for the identification and characterization of clinical and neurological features in patients with GBS and its subtypes with suspected previous ZIKV, CHIKV or DENV infection, during an outbreak in 2015.

METHODS

Study Design

We propose a hospital surveillance study in patients followed in neurological units of two reference hospitals in Salvador, Bahia, Brazil, from May 2015 to April 2016. The study population were patients with GBS or its subtypes coming from emergencies and outpatient neurology sectors of participating hospitals.

Inclusion criteria

Patients with symptoms compatible with GBS or its subtypes were admitted in emergencies or outpatient neurology sector of the participating hospitals during the ZIKV, CHIKV and DENV outbreak in 2015.

The diagnosis of SGB, Miller-Fisher syndrome (MFS) and other subtypes were predetermined by disease-specific criteria1.

Exclusion criteria

Patients or legal responsible parents who did not consent to participation or patients with symptoms probably related to other plausible causes such as cancer, bacterial infection, trauma, intoxication, metabolic diseases and other medical condition were excluded from the study.

Data collection

Collection of clinical, epidemiological and laboratory data was performed at hospital admission and at outpatient visits. Patients were monitored and evaluated during hospitalization on different days of visits and questioned about the improvement of the symptoms. Hughes scale (HFS) was used to evaluate the impairment and severity of the neurological symptoms. The scale consist of seven items (0-6), the highest values corresponding to the greatest neurological dysfunction 21. The House-Brackmann scale was used to evaluate the severity of facial paralysis in patients affected by this manifestation. It is a 6-item scale (1-6), the greatest dysfunction related to higher scores 22.

Patients were examined by the participating neurologist, who recorded the clinical data in a pre-established and standardized questionnaire. Clinical data were evaluated during the hospital stay and after hospital discharge as outpatient evaluation.

Biological samples

Serum and cerebrospinal fluid (CSF) samples were collected from the study hospitals by the participating neurologist. The samples were identified and processed for shipment to IGM-FIOCRUZ. They were conditioned and transported in refrigerated temperature.

Serological diagnosis

Serological diagnosis for arbovirus was performed in all samples collected for the detection of anti-DENV, anti-CHIKV and anti-ZIKV IgG and IgM antibodies by the enzyme immunoassay (ELISA) The commercial kits Euroimmun® Dengue IgM, Dengue IgG, Chikungunya IgM, Chikungunya IgG and Zika IgG (Euroimmun, Lübeck, Germany) were used for the detection of antibodies against DENV, CHIKV, and ZIKV according to the manufacturer's instructions. The detection of anti-Zika IgM antibodies was performed by in-house capture ELISA using a kit provided by the Centers of Disease and Control (CDC-Atlanta)23.

As a differential diagnosis, serologies were performed for toxoplasma, rubella, cytomegalovirus, Herpes, Syphilis and HIV and HTLV. For the detection of specific IgG and / or IgM for each infectious agent, indirect ELISA and / or capture ELISA was used. The tests were performed, following the manufacturer's protocol, through the automation or semi-automation apparatus.

Electrodiagnostic study

Electromyography (EMG) and nerve conduction studies (NCS) was performed in patients with suspected GBS, MFS or other neuromuscular disorders. This exam was performed by expert neurologist in electrophysiology. The exams were performed at no additional cost to patients.

The Neuropack® MEB-9200, brand of 4-channel PE / EMG Nihon Kohden® brand (evoked potential / measurement of electromyography) was used for the exams.

Electrophysiological assessment was by standard electromyography techniques including motor nerve conduction studies of the median nerve (recording of the abductor pollicis brevis), the ulnar nerve (recording of the abductor digiti minimi), and the peroneal nerve (recording of the extensor digitorum brevis), as well as sensory nerve conduction studies in radial and sural nerves.

Ethical considerations

All participants agreed to participate in the study and signed a Consent Form, containing explicit information about the nature and objectives of the research, in language appropriate to the educational level of the study population.

This project was submitted and approved by the ethics committee of IGM-Fiocruz (1,400,224). The risks to the volunteers were minimal as it involves routine procedures such as obtaining peripheral blood or collecting CSF. The refusal to participate of the study did not imply any damage to patient's treatment. The CSF and EMG exams were part of the diagnostic arsenal performed in the care routine.

Results of diagnostic tests for arbovirus were reported to patients at the time of outpatient reassessment.

Statistical analysis

It was used REDCap program 6.14.0 - © 2016 Vanderbilt University for data entry and the statistical analyzes were performed in the IBM-SPSS version 21 program. The Descriptive analyzes of the study population were initially performed. Categorical data were described using proportions with 95% confidence intervals and the numerical data described by mean and standard deviation (or variance). The Hughes and House-Brackmann scores was used as continuous variables to calculate means in the 2 different groups (admission X re-evaluation in 30 days). These scores were categorized to show patients' functional levels. The categorization follows: mild disability (Hughes 0-2) and severe disability (Hughes 3-5); mild facial palsy (House-Brackamnn 1-3), severe facial palsy (House-Brackmann 4-6).

Categorical data were compared using the Chi-square test (x2) or Fisher's exact test.

RESULTS

During the study period, a total of 14 patients with diagnosis of GBS or MFS were accompanied. All but one patient was from Salvador (93%).

The median age of the patients included was 40,5 years (IQR 28-52), with a slightly higher prevalence of females (57%). Most common viral symptoms were polymyalgia skin rash, arthralgia, pruritus, paresthesia in the beginning of viral manifestations (57%), headache and fever (42%). Symptoms such as conjunctivitis and edema in the extremities were uncommon (7% and 14%, respectively). Median duration of viral symptoms was 4 days (IQR 3-6,5).

Median time between viral and neurological symptoms was 10 days (IQR 9-14). Median time between onset of neurological symptoms and hospital evaluation was 4 days (IQR 1-10). Mean length of hospital stay was 9 days (IQR 5-17) (table 1).

Ten patients were diagnosed with GBS and most of them (7 patients) presented as classic GBS; 3 patients presented as subtypes – bifacial weakness and paraesthesias and paraparetic GBS. Four patients were diagnosed as MFS and only 1 presented the complete syndrome, while the other patients presented as acute ataxic neuropathy subtype.

Mean age of GBS patients was 43 years, with predominance of symptoms compatible with acute polyneuropathy: paresthesia (socks and gloves pattern), muscle weakness, hyporeflexia and facial paralysis. Other manifestations such as dysarthria, dysphagia and ataxia were also present. Four patients with MFS had a mean age of 43 years and all presented predominant symptoms of ataxia and paresthesia in hands and feet, associated with sensory disturbance. Only two cases had a manifestation of muscular weakness predominantly brachial cervical pattern. In 25% of the patients, there were altered ocular motricity, headache, hyporeflexia or dysphagia, and none of them had facial paralysis or inability to walk (table 1).

Regarding the degree of clinical severity, the majority (70%) of GBS patients presented scores between 3-5 on HFS, denoting a greater severity of disease. All patients with GBS were hospitalized and 70% of them were admitted to intensive care unit. Despite the severity of the symptoms, none of these patients underwent mechanical ventilation; all survived and were discharged home. Eight patients were treated with intravenous immunoglobulin (IVIG) therapy (80%) and the mean number of days between onset of neurological symptoms and initiation of IVIG infusion was 9 days and mean time between hospital admission and onset of IVIG was 3 days (variance 1-10 days). Only 1 of the MFS patients presented with the severe form of the disease (HFS >2), and no IVIG therapy was done. The mean length of hospital stay was 11 days for patients with GBS and 12 days in those with MFS.

Ten patients were re-evaluated 30 days after discharge. Of these, 8 were diagnosed with GBS (80%) and 2 MFS (20%). All patients were fully functional when evaluated 30 days after discharge, with HSF <2. Mean HFS on admission was 2.87 and when evaluated 30 days later it was 0.25, showing a decrease of 2 points on average ($p = 0.0001$). Seven of the re-evaluated patients had severe disfunction of facial nerve on admission (HBS>4) although all of them recovered drastically when examined 30 days after discharge (HBS <3). Mean difference between HBS on admission and re-evaluation was 3,43 points ($p <0,001$).

Nine patients (64%) underwent EMG. Of these, 8 had diagnosis of GBS and 1 with MFS. Motor nerve conduction study showed the same pattern in most tested nerves, with prolonged

distal latencies and conduction slowing, but with no reduction of the distal compound muscle action potential (CMAP) amplitude and conduction velocity of sensory potentials were mildly altered in radial and sural nerves, which is compatible with acute inflammatory demyelinating polyneuropathy (AIDP), with conduction block pattern (table 2). Eight seven percent of them had demyelination of the facial nerves.

ZIKV infection was observed in 78% of the patients analyzed with positivity for anti-ZIKV IgM or IgG. Most of the patients in this case series had positivity for anti-dengue IgG (78%). Positivity for both anti-ZIKV IgM and anti-DENV IgM was not seen. Serology profile is detailed in table 3.

CHIKV was detected with anti-CHIKV IgM or IgG in only 2 patients accompanied (14%). All of them had also ZIKV positivity for IgM or IgG in serologic tests.

All of the patients were tested for HIV, HTLV, CMV, EBV, HCV, HBV, syphilis and none of them had positivity for any of these tests.

DISCUSSION

The term GBS is used to describe a broad spectrum of acute autoimmune neuropathies. This disease usually affects motor function usually beginning distally and progressing proximally over a 4-week period. Most common clinical manifestation are generalized weakness, areflexia, sensory and autonomic disturbances and usually involves cranial nerves. GBS presentation can vary widely since various subtypes were identified over time (MFS and other subtypes). MFS is a variant acute idiopathic polyneuritis characterized by ophthalmoplegia, areflexia and ataxia. This subtype is likely a midbrain form of GBS. Some variants can be rare such as acute ptosis or acute mydriasis, although other forms such as paraparetic GBS, bifacial weakness with paraesthesias, pharyngeal-cervical-brachial weakness can be common but usually unrecognized by many clinicians 1. Half of the patients followed in this study was composed by GBS subtypes, such as acute ataxic neuropathy and bifacial weakness with paraesthesias. These variants can be misdiagnosed as other diseases such as Bell's palsy or cerebellar disfunction if physicians are unaware of clinical myriad of GBS.

About two thirds of the patients with GBS report an antecedent acute infectious illness and numerous infectious agents are associated with this syndrome 17. Association with arboviruses, such as DENV, CHIKV and ZIKV, have been reported 4,5. The clinical picture of GBS associated with ZIKV and other arbovirus was seen to be similar to other cases of GBS cases, however, there is a perception that there are more cases of variants, rapid course, a short

plateau phase and high proportion of facial nerve involvement, as we could observe in our case series 24.

Most of the GBS patients in this study presented on admission with HFS scores of 3 or more (70%) denoting a severe disease. This was also pictured by high frequency of facial palsy (80%) with HBS >4 (88%). Patients with MFS presented with milder disease, with HFS lower than 3 predominating in this group (75%). None of MFS patients had facial palsy, as expected.

All patients re-evaluated 30 days after hospital discharge had mild disabilities represented by low functional scores (HFS<2 and HBS <3). This contrasts with other GBS studies that show that patients with higher functional scores tend to have low rates of recovery 25. We can hypothesize that this good recovery could be due to prompt treatment with IVIG infusion, which in our series was only of 3 days (median) since admission to infusion (9 days since neurological symptoms and infusion) or due to a peculiarity of arboviral triggered GBS syndrome 24.

Previous infection by ZIKV was confirmed by the presence of anti-ZIKV IgM and IgG antibodies. Since there was no evidence of circulation of ZIKV before the study period, and the median time difference between viral and neurological manifestation was long (10 days), we can infer that presence of anti-ZIKV IgG marks recent previous infection. Seventy-eight percent of the patients studied had evidence of ZIKV infection. Many studies suggests that GBS and other neurological syndromes are strongly associated with ZIKV26.

Not all the cases can be attributed to ZIKV, once other co-circulating arboviruses (CHIKV and DENV) have the potential for neurological complications. Only 2 patients with GBS or its variants (14%) had positivity for previous CHIKV infection (IgM or IgG). All of them had evidence of other arboviral infection such as ZIKV.

None of the patients had positivity for anti-DENV IgM antibodies. Most of them had previous evidence of DENV infection with 78% of anti-DENV IgG positivity. As the present series demonstrate, in the FP case-control study, most individuals had prior DENV infection, regardless of whether they were in the control or study group; this information weakens the idea that individuals previously infected with DENV might be more susceptible to neurological manifestations when infected with ZIKV 17.

CSF analysis showed presence of albuminocitological dissociation in 90% of patients with GBS and 75% of the MFS cases. These characteristics was also observed in 2 case-control studies previously published in FP and Colombia 17,27.

Prolonged distal latencies and reduced distal CMAP, in EMG study, at admission, can be interpreted as demyelinating conduction slowing and block, leading to the classification of

the GBS pattern as acute AIDP with axonal degeneration. Most of the patients (87%) had demyelinating polyneuropathy and axonal secondary degeneration of the facial nerves. The only MFS patient submitted to ENMG also had a pattern of AIDP, but no facial nerve disfunction. The pattern of demyelination found in the present study is similar to the pattern seen in the case-control study conducted in Colombia 27. However, the most relevant study showing association between GBS and ZIKV revealed axonal polyneuropathy pattern on ENMG of its subjects 17.

In conclusion, most of the patients had evidence of previous ZIKV (78%) and CHIKV (14%) infection. There was a high proportion of facial palsy (80% of GBS subgroup) and a great clinical recovery on 30 days re-evaluation. EMG findings were compatible with AIDP differing from previous case-control study which showed a prevalence of axonal polyneuropathy. Because the probable association between emergent arboviruses and GBS, and a wide variety of clinical subtypes, clinicians and other healthcare professionals must be alert and vigilant in regions affected by arbovirus outbreaks.

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Tables

Table 1. Clinical characteristics of 14 patients with GBS

Characteristics	n (%) / Median (IQR)
Mean age in years (variance)	40,5 (28-52)
Women	8 (57)
Previous viral syndrome	
Polymyalgia	8 (57)
Rash	8 (57)
Arthralgia	8 (57)
Pruritus	8 (57)
Paresthesia at the onset of symptoms	8 (57)
Headache	6 (42)
Fever	6 (42)
Edema in limbs	2 (14)
Conjunctivitis	1 (7)
Duration of viral symptoms (days)	4 (3-6,5)
Time between viral and neurological symptoms (days)	10 (9-14)
Time between neurological symptoms and admission (days)	4 (1-10)
Length of hospital stay (days)	9 (5-17)
Guillain-Barré syndrome	10 (71)
GBS patients features	
Paresthesia	9 (90)
Sensory disturbance	9 (90)
Muscle weakness	9 (90)
Areflexia/ hyporeflexia	9 (90)
Facial palsy	8 (80)
Dysarthria	7 (70)
Inability to walk	5 (50)
Dysphagia	5 (50)
Ataxia	3 (30)
Functional Hughes scale on admission (0-2) – mild disease	3 (30)
Functional Hughes scale on admission (3-5) – severe disease	7 (70)
Treatment with IVIG infusion	8 (80)

Number of days between admission and IVIG infusion	3 (1-10)
Number of days between neurological symptoms and IVIG infusion	9 (1-25)
Admission to ICU	7 (70)
Need for orotracheal intubation	0
Mean length of stay	11 (5-20)
Miller Fisher syndrome	4 (29)
MFS patients features	
Paresthesia	4 (100)
Ataxia	4 (100)
Muscle weakness	2 (50)
Dysphagia	1 (25)
Areflexia/ hyporeflexia	1 (25)
Facial palsy	0
Inability to walk	0
Functional Hughes scale on admission (0-2) – mild disease	3 (75)
Functional Hughes scale on admission (3-5) – severe disease	1 (25)
Treatment with IVIG infusion	0
Admission to ICU	3 (75)
Need for orotracheal intubation	0
Mean length of stay	12 (6-23)

GBS = Guillain-Barré syndrome

Table 2. Motor nerve conduction parameters (mean values) on EMG after onset of Guillain-Barré syndrome

	Median			Ulnar			Fibular		
	DML (ms)	Ampli (mV)	MCV (m/s)	DML (ms)	Ampli (mV)	MCV (m/s)	DML (ms)	Ampli (mV)	MCV (m/s)
Reference value*	N <4,5	N > 4,1	N > 49	N <3,7	N > 7,9	N > 52	N <6,5	N > 1,3	N > 38
Total ENMG (9)	7,35	9,49	49,65	4,17	7,37	43,39	6,02	4,61	38,99
Before 1º month (3)	6,78	7,95	48,08	4,25	4,13	39,10	5,75	3,43	36,78
After 1º month (6)	7,78	10,65	50,84	4,13	9,80	46,60	6,15	5,20	40,10
Median time in days between neurological symptoms and ENMG (IQR)				40 (22,5-45,5)					

EMG = electromyography. DML=distal motor latency. Ampli=amplitude of the distal compound muscle action potential. MCV=motor conduction velocity. *Reference values are as recommended by the American Association of Electrodiagnostic Medicine).

Table2: Pattern of detection of zika and chikungunya IgG and IgM in 14 patients with GBS during triad arboviral outbreak 2015-2016

		ZIKV positive			ZIKV IgM/ZIKV IgG				ZIKV IgM/ DENV IgM			
	N	IgM or IgG	IgM	IgG	+/+	+/-	-/+	-/-	+/+	+/-	-/+	-/-
GBS	10	7 (70%)	4 (40%)	7 (70%)	4	0	3	3	0	4	0	6
MFS	4	4 (100%)	3 (75%)	4 (100%)	3	0	1	0	0	3	1	0

		CHIKV positive			CHIKV IgM/CHIKV IgG				CHIKV IgM or IgG/ ZIKV IgM or IgG			
	N	IgM or IgG	IgM	IgG	+/+	+/-	-/+	-/-	+/+	+/-	-/+	-/-
GBS	10	1 (10%)	1 (10%)	1 (10%)	1	0	0	9	1	0	6	3
MFS	4	1 (25%)	1 (25%)	0 (0)	0	1	0	0	1	0	3	0

		DENV positive		DENV IgM/DENV IgG				DENV IgM/ ZIKV or CHIV IgM or IgG			
	N	IGM	IgG	+/+	+/-	-/+	-/-	+/+	+/-	-/+	-/-
GBS	10	0 (0)	7 (70%)	0	0	7	3	0	0	7	3
MFS	4	1 (25%)	4 (100%)	1	0	3	0	1	0	4	0

Date ar n (%) or n. GBS = Guillain-Barré syndrome; MFS = Miller Fisher syndrome; ATP = Acute transient polyneuritis; ENC = encephalitis; OMAS = Opsoclonus myoclonus ataxia syndrome; MYEL = myelitis; ADEM = Acute demyelinating encephalomyelitis; CTS = Carpal tunnel syndrome

8. ARTIGO 5: Neurological syndromes during a concurrent outbreak of Zika, Chikungunya and Dengue virus infections in Salvador, Bahia, Brazil

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Descrição das diferentes síndromes neurológicas, em corte transversal, em pacientes admitidos em hospitais terciários durante a tríplice epidemia arboviral.

Neurological syndromes during a concurrent outbreak of Zika, Chikungunya and Dengue virus infections in Salvador, Bahia, Brazil

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SUMMARY

Dengue, zika and chikungunya viruses usually cause mild exanthematic diseases, but disorders like Guillain-Barré syndrome (GBS), encephalitis and others were previously reported. Methods: Cross-sectional observational study in patients with neurological syndromes from May 2015 to April 2016 in Brazil. Blood, serum and CSF samples were collected for virus identification. Serologic studies and RT-PCRq was performed. Results: Twenty-nine patients were followed and most of them had diagnosis of GBS (48%). Other diagnosis was acute transient polyneuritis, myelitis, encephalitis and OMAS. Zika was present in 79% and chikungunya in 31% of the patients.

INTRODUCTION

Arboviruses are viruses transmitted biologically between vertebrates by arthropods insects - mosquitoes or ticks – with obligatory replication within the vectors [1]. In Brazil, several of these arboviruses circulate in urban and peri-urban areas, some causing febrile exanthematic disease such as dengue virus (DENV), Oropouche (OROV), mayaro (MAYV) and yellow fever (YFV)[2]. A variety of these viruses are circulating in Brazil, seen in several studies of serum-prevalence and surveillance of exanthematic diseases[3].

Zika virus (ZIKV) is an emergent flavivirus transmitted by Aedes aegypti mosquitoes. The first documented human case of ZIKV infection was reported in Nigeria in 1954, with a number of sporadic cases reported in Africa and Asia in subsequent years [4]. More recently, ZIKV re-emerged, causing major outbreaks in Micronesia in 2007, French Polynesia in 2013 and New Caledonia in 2014 [5]. ZIKV was initially detected in Northeastern Brazil on March 2015 [6,7] and has rapidly spread throughout South and Central America and the Caribbean [8].

Chikungunya virus (CHIKV), is an alphavirus first described in Africa in 1952 and was spread to other countries after 2005 when a large outbreak in the Reunion Islands occurred [9]. Its arrival in Brazil occurred in 2014 with a huge dissemination throughout the country [10].

The DENV is a flavivirus that circulates in Brazil since 1845. DENV is also transmitted by Aedes. mosquitoes. This mosquito was eradicated from Brazil until 1976 re-infestation of peri-urban areas and then various outbreaks of DENV occurred, culminating in cocirculation of 4 serotypes (DEN1 - DEN4) since 2010 [11].

Many arboviruses are known to be related to neurological diseases such as West Nile virus (WNV), Saint Louis encephalitis virus (SLEV), Japanese encephalitis virus (JEV). DENV, ZIKV and CHIKV viruses, recently co-circulating in Brazil, are known to cause mild exanthematic diseases or acute febrile syndromes, but many neurological disorders such as Guillain-Barré syndrome (GBS), encephalitis, myelitis , muscular manifestations, opsoclonus-myoclonus ataxia syndrome (OMAS), and others were previously reported [12,13].

We propose a cross-sectional observational study for the identification and characterization of clinical manifestation of neurologic disorders in patients with suspected previous arboviral infection admitted to two neurological reference hospitals in Salvador, Bahia, Brazil.

Methods

Study Design

We proposed a cross-sectional observational study in patients assisted in neurological units of two reference hospitals in Salvador, Bahia, Brazil, from May 2015 to April 2016. The study population were patients with acute neurological syndromes admitted to emergencies and outpatient neurology sectors of participating hospitals. Two tertiary hospitals with reference in neurology were selected: Hospital Geral Roberto Santos (HGRS) and Hospital Santa Izabel (HIS).

Inclusion criteria

Patients with symptoms compatible with GBS, encephalitis, myelitis, polyneuropathies, movement disorders, among other neurological diseases of acute onset that were admitted in emergencies or outpatient neurology sector of the participating hospitals during the ZIKV, CHIKV and DENV outbreak in 2015-2016.

The diagnosis of GBS, Miller-Fisher syndrome (MFS) and its variants [14], encephalitis [15], myelitis [16], OMAS [17], transient polyneuritis (ATP)[18], ADEM [19] and Carpal Tunnel Syndrome (CTS) [20] was predetermined by disease-specific criteria.

Exclusion criteria

Patients or legal responsible parents who did not consent to participation or patients with symptoms probably related to other plausible causes such as cancer, bacterial infection, trauma, intoxication, metabolic diseases and other medical condition were excluded from the study.

Data collection

Clinical, epidemiological and laboratory data were collected at hospital admission, during hospitalization and at outpatient visits. Serum, cerebrospinal fluid (CSF) and urine samples were collected by the neurologist also. Patients were examined by the participating neurologist, who recorded the clinical data in a pre-established and standardized questionnaire.

Biological samples

Serum, urine and CSF samples were collected at admission.

Serological diagnosis

Serological diagnosis for arbovirus was performed in all samples collected for the detection of anti-DENV, anti-CHIKV and anti-ZIKV IgG and IgM antibodies by the enzyme

immunoassay (ELISA) The commercial kits Euroimmun® Dengue IgM, Dengue IgG, Chikungunya IgM, Chikungunya IgG and Zika IgG (Euroimmun, Lübeck, Germany) were used for the detection of antibodies against DENV, CHIKV, and ZIKV according to the manufacturer's instructions. The detection of anti-Zika IgM antibodies was performed by in-house capture ELISA using a kit provided by the Centers of Disease and Control (CDC-Atlanta)[21].

As a differential diagnosis, serologies were performed for toxoplasma, rubella, cytomegalovirus, Herpes, Syphilis and HIV and HTLV. For the detection of specific IgG and / or IgM for each infectious agent, indirect ELISA and / or capture ELISA was used. The tests were performed, following the manufacturer's protocol, through the automation or semi-automation apparatus.

Molecular diagnosis

Serum, urine and CSF samples were subjected to RNA extraction according to the QIAmp Viral RNA minikit (QIAGEN) kit manufacturer's instructions. After isolation of the RNA, the samples were dosed to know the concentrations of this nucleic acid, using the NanoDrop 2000

The RNA isolated was used to quantitate Real Time PCR (qPCR), using the Rotor-Gene Q (QIAGEN) equipment, using the Quantinova kit (QIAGEN), for the detection of ZIKV in samples clinics. The presence of ZIKV was detected by the amplification of the viral envelope genes using primers 5'CCGCTGCCCAACACAAG3 '(sense) and 5'CCACTAACGTTCTTTTGCAGACAT3' (antisense), and the probe FAM-5'AGCCTACCTTGACAAGCAGTCAGACACTCAA3 'recommended by CDC (FAYE et al. (1998). In addition, primer pairs 5'TTGGTCATGATACTGCTGATTGC3 '(sense) and 5'CCTTCCACAAAGTCCCTATTGC3' (antisense) were used with the probe FAM-5'CGGCATACAGCATCAGGTGCATAGGAG3 'or 5'AARTACACATACCARAACAAAGTGGT3' (sense) and 5'TCCRCTCCCYCTYTGGTCTTG3 '(anti), with the probe FAM-5 'CTYAGACCA+G+C+T+G+AAR 3', for amplification of samples with very high Ct values. In all reactions the RNA extracted from the viral culture supernatant was used as a positive control.

Electrodiagnostic study

Electromyography (EMG) and nerve conduction studies was performed in patients with suspected GBS, MFS or other neuromuscular disorders. It was performed by neurologist expert in electrophysiology. The exams were performed at no additional cost to patients.

Neuropack® MEB-9200, brand of 4-channel PE / EMG Nihon Kohden® brand (evoked potential / measurement of electromyography) was used for the exams.

Sensory and motor nerves, F-waves and H-reflexes of the upper limbs, lower limbs, and facial nerve were studied in all patients submitted to the examination. Needle electromyography was also performed in patients without contraindications.

Ethical considerations

All subjects agreed to participate in the study and signed a Consent Form, containing explicit information about the nature and objectives of the research, in language appropriate to the educational level of the study population.

This project was submitted and approved by the ethics committee of IGM-FIOCRUZ. The risks to the volunteers were minimal as it involves routine procedures such as obtaining peripheral blood, collecting CSF and urine. The refusal to participate of the study did not imply any damage to patient's treatment. The CSF and ENMG exams were part of the diagnostic arsenal performed in the care routine.

Results of diagnostic tests for arbovirus were reported to patients at the time of outpatient reassessment.

Statistical analysis

It was used REDCap program 6.14.0 - © 2016 Vanderbilt University for data entry and the statistical analyzes were performed in the IBM-SPSS version 21 program. Descriptive analyzes of the study population were initially performed. Categorical data were described using proportions with 95% confidence intervals and the numerical data described by mean and standard deviation (or variance). Hughes functional scale (HFS) was used to evaluate the impairment and severity of the neurological symptoms. The scale consist of seven items (0-6), the highest values corresponding to the greatest neurological dysfunction [22]. HFS was used as continuous variables to calculate means in the 2 different groups (during hospitalization X reevaluation in 30 days). These scores were categorized to show patients' functional levels - mild disability (Hughes 0-2) and severe disability (Hughes 3-5).

RESULTS

During the study period, a total of 29 patients were accompanied, 16 of them from the HGRS and 13 from the HSI. Twenty-three patients (79%) were from Salvador and 6 (21%) patients from the country-side.

Median age of the patients included was 38 (IQR 22-68) years, with a higher prevalence of females (65%). Ninety-three percent of individuals reported previous viral symptoms during a median of 5 (IQR 2-11) days. The most common previous symptoms were polymyalgia (72%), skin rash (65%), arthralgia (62%), pruritus (58%), paresthesia in the beginning of viral manifestations, headache and fever (55%). Symptoms such as conjunctivitis and edema in the extremities were uncommon (27% and 26%, respectively). (table 1)

Twenty-three patients (79%) were evaluated in the hospital environment, admitted to neurological units, and the median time between onset of neurological symptoms and hospital evaluation was 4 days. Median length of hospital stay was 10 days. Six patients (21%) were evaluated as outpatients in hospitals ambulatories.

Most of the patients presented as GBS (34%) or MFS (14%). Most of the GBS cases presented with the classic form of the disease (50%) while the other presented as MFS (7%) or other variants (43%).

Several other neurological manifestations were observed such as acute transient polyneuritis (5 patients - 17%), encephalitis (3 patients - 10%), myelitis (2 patients - 7%), CTS (2 patients - 7%), OMAS (2 patients - 7%) and ADEM (1 patient - 3%) (table 2).

Twenty-two patients were submitted to CSF puncture. All patients with GBS and MFS had cerebrospinal fluid analysis. The presence of albuminocytologic dissociation occurred in 90% of patients with GBS and 75% in patients with MFS.

Eleven patients underwent EMG - 8 GBS, 1 MFS and 1 ATP. All patients with GBS who performed EMG had acute inflammatory demyelinating polyneuropathy (AIDP), with conduction block pattern and 87% of them had demyelination of the facial nerves. MFS patient had a pattern of nerve demyelination in superior and inferior limbs, without facial nerve disturbance. Two patients diagnosed with ATP had only bilaterally median nerve demyelination pattern at the wrist level, compatible with carpal tunnel syndrome, and no other abnormality.

ZIKV RT-PCRq was tested in serum samples of 28 patients and all of them resulted negative. ZIKV infection was observed in 22 (79%) of the serum samples analyzed. Twelve of them (54%) had positivity for anti-Zika IgM, confirming recent infection by this agent. Considering the 14 patients with GBS and MFS, 11 of them (78%) had positivity for anti-ZIKV

IgM or IgG. Concomitant positivity for anti-zika IgM and anti-dengue IgM was seen in only 2 cases (6%). Serology profile is detailed in table 3.

CHIKV was detected with anti-CHIKV IgM or IgG in 9 of 29 (31%) cases. Most of them (7 of 9 – 78%) had ZIKV also positivity for IgM or IgG in serologic tests. – table 3

Only 6 patients (20%) had positivity for anti-dengue IgM antibodies, but all of them had positivity for anti-ZIKV or anti-CHIKV (IgM or IgG) antibodies as well. Previous DENV infection was seen 82% of the patients (anti-DENV IgG positivity)– table 3.

All of the patients were tested for HIV, HTLV, CMV, EBV, HCV, HBV, syphilis and none of them had positivity for any of these tests.

DISCUSSION

DENV is circulating in Brazil since 1845 and several outbreaks have been occurred. Since 2010, four serotypes (DENV1-4) are co-circulating in this country, challenging Brazilian public health system for controlling and preventing new epidemics [23]. Since the introduction of CHIKV in 2014 and ZIKV in 2015 new concerns raised about complications of this triad co-circulation [13]. In 2016, 277,882 probable cases of CHIKV were recorded, and in 2015 20,901 cases, with the highest incidence in the northeast region. At the same period (since 2015 to epidemiological week 52 in 2016), all Brazilian states and federal district have registered cases of ZIKV infection with a total of 2,015,319 (incidence rate of 105.3 cases/100,000 inhabitants) [24].

Neurological complications related to DENV, CHKV or ZIKV were thought to be uncommon, but several reports were made during latest outbreaks of these arboviral diseases [13]. Since 2015, in Brazil, a growing number of neurological syndromes, including GBS, were seen following the pattern of ZIKV and CHIKV outbreak [25]. Numerous GBS cases were notified in Bahia, Brazil, accounting for 214 probable cases from 2015 to epidemiological week 45 of 2017. Most of the cases were diagnosed in 2015 during ZIKV outbreak (177 probable cases) [24].

Guillain-Barré syndrome is an acute, immune-mediated polyradiculoneuropathy typically occurring after minor viral and bacterial infections. Motor function is usually affected, beginning distally and progressing proximally over up to a 4-week period. Clinical manifestation consists in generalized weakness, areflexia, and a varying degree of sensory disturbances and involvement of cranial nerves. This disease can exist as several clinical subtypes with different neurological features and presentations, such as MFS, Bickerstaff syndrome and other subtypes. Despite pathophysiology is not completely understood, GBS mostly occur 2–8 weeks after an infection. [14].

We were able to examine and follow 29 patients with different neurological syndromes. Study was performed in 2 hospitals that were references to patients with neurological complications during the arboviral outbreak in 2015 in Bahia.

The female predominance (65%) in this study differs from other case series. Mean age was like other reports (41 years). The most prevalent neurological diagnosis was GBS and its variants (MFS and others) accounting for 48% of the cases [25–27]. Other neurological syndromes, varying from mild and benign course diseases as PTA and CTS to severe and life-threatening diseases such as encephalitis, myelitis, ADEM and OMAS. These maladies were already listed as potential complications of arboviral diseases in previous studies [13,25,28].

Previous infection by ZIKV was confirmed by the presence of anti-ZIKV IgM and IgG antibodies. Since there was no evidence of circulation of ZIKV before the study period, and the mean time difference between viral and neurological manifestation was long (14 days), we can infer that presence of anti-ZIKV IgG marks recent previous infection. Seventy-five percent of the patients studied had evidence of previous ZIKV infection. Previous studies suggests that GBS and other neurological syndromes are strongly associated with ZIKV[29].

Although, not all the cases can be attributed to ZIKV, once the other co-circulating arboviruses (CHIKV and DENV) have the potential for neurological complications. Nine of the patients in the present study (31%) had positivity for previous CHIKV infection (IgM or IgG). Most of the patients (77%) had evidence of other arboviral infection such as ZIKV. Only 2 CHIKV positive patients presented with GBS or its variants. During the study period it was thought that GBS was only related to ZIKV, but as seen in other reports, CHIKV can also be and triggering factor to GBS [30]. The evidence that CHIKV was the unique arbovirus linked to the neurological complication was seen in 2 patients with ATP.

Most of the patients had positivity for anti-DENV IgG (82%). All patients with anti-DENV IgM also had IgM against ZIKV, suggesting that the anti-DENV IgM response could result from cross-reactivity. A similar proportion of anti-DENV IgM and anti-ZIKV IgM positivity was found in the Polynesian case-series [26].

CSF analysis showed presence of albuminocitological dissociation in 90% of patients with GBS and 75% of the MFS cases. There was no change in the CSF study in the 2 patients with PTA who underwent the test (table x). This characteristic was also observed in 2 case-control studies previously published in French Polynesia and Colombia [26,27].

All patients with GBS and MFS had demyelinating pattern polyneuropathy in EMG. The pattern of demyelination found in the present study is similar to that seen in the case-control study conducted in Colombia [27]. However, the most relevant study showing association between GBS and ZIKV revealed axonal polyneuropathy pattern on electrodiagnostic study [26].

Although most of the patients accompanied in this study were from Salvador, we cannot fully attribute a role of ethnicity in triggering GBS or other immune related neurological syndromes, once these syndromes were incident in other outbreaks oversea (French Polynesia, El Salvador, Colombia) were population are multi-ethnic as ours [26].

In conclusion, this study shows that during an overwhelming epidemic of 3 different arbovirus in our city, a multiplicity of severe neurological complication occurred. GBS, MFS and its subtypes were the predominant diseases, but healthcare professional need to be aware

of the other possible immune mediated neurological maladies such as myelitis, encephalitis, OMAS and ADEM. Not all neurological syndromes are potentially severe as aforementioned. We described some cases of mild sensory polyneuropathy (ATP) and isolated CTS, which had benign clinical course. Because the potential association between emergent arboviruses and neurological syndromes, clinicians must be alert and vigilant with respect to neurological complications in regions affected by arbovirus outbreaks.

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Tables

Table 1. Clinical characteristics of 29 patients with acute neurological syndromes 2015-2016

Characteristics	n (%) / Median (IQR)
Age in years	38 (21-68)
Women	19 (65)
Previous viral syndrome	
Polymyalgia	21 (72)
Rash	19 (65)
Arthralgia	18 (62)
Pruritus	17 (58)
Paresthesia at the onset of symptoms	16 (55)
Headache	16 (55)
Fever	16 (55)
Conjunctivitis	8 (27)
Edema in limbs	7 (26)
Duration of viral symptoms (days)	5 (2-11)
Time between viral and neurological symptoms (days)	11 (9-16)
Time between neurological symptoms and admission (days)	4 (1-10)
Length of hospital stay (days)	10 (6-22)
Lumbar puncture results	
GBS	10 (100%)
Proteins (mg/dL)	102,2
Increased CSF protein concentration (>40mg/dL)	9 (90%)
Cells (per mm^3)	10
MFS	4 (100%)
Proteins (mg/dL)	217
Increased CSF protein concentration (>40mg/dL)	75%
Cells (per mm^3)	27
ATP	2 (40%)
Proteins (mg/dL)	26
Increased CSF protein concentration (>40mg/dL)	0 (0)
Cells (per mm^3)	26

Table 2. Neurological syndromes in 29 patients during a triad arboviral outbreak in Salvador/Bahia/Brazil

Characteristics	n (%)
Neurological syndromes	
Guillain-Barré syndrome (GBS)	10 (34)
Acute transient polyneuritis (ATP)	5 (17)
Miller Fisher Syndrome (MFS)	4 (14)
Encephalitis	3 (10)
Myelitis	2 (7)
Opsoclonus-myoclonus ataxia syndrome (OMAS)	2 (7)
Carpal tunnel syndrome (CTS)	2 (7)
Acute demyelinating encephalomyelitis (ADEM)	1 (3)

Table3: Pattern of detection of zika, chikungunya and dengue IgG and IgM in 29 patients with neurological complications during triad arboviral outbreak 2015-2016

		ZIKV positive			ZIKV IgM/ZIKV IgG				ZIKV IgM/ DENV IgM			
	N	IgM or IgG	IgM	IgG	+/+	+/-	-/+	-/-	+/+	+/-	-/+	-/-
TOTAL	29	22 (76%)	12 (41%)	18 (62%)	12	0	10	7	2	10	3	14
GBS	10	7 (70%)	4 (40%)	7 (70%)	4	0	3	3	0	4	0	6
MFS	4	4 (100%)	3 (75%)	4 (100%)	3	0	1	0	0	3	1	0
ATP	5	2 (40%)	1 (20%)	2 (40%)	1	0	1	3	0	1	0	4
ENC	3	3 (100%)	2 (67%)	3 (100%)	2	0	1	0	2	0	0	1
OMAS	2	2 (100%)	2 (100%)	2 (100%)	2	0	0	0	0	2	0	0
MYEL	2	2 (100%)	0 (0)	2 (100%)	0	0	2	0	0	0	2	0
ADEM	1	1 (100%)	1 (100%)	1 (100%)	1	0	0	0	1	0	0	0
CTS	2	2 (100%)	0	2 (100%)	0	0	2	0	0	0	0	2

		CHIKV positive			CHIKV IgM/CHIKV IgG				CHIKV IgM or IgG/ ZIKV IgM or IgG			
	N	IgM or IgG	IgM	IgG	+/+	+/-	-/+	-/-	+/+	+/-	-/+	-/-
TOTAL	29	9 (31%)	7 (24%)	6 (20%)	4	3	2	10	7	2	15	5
GBS	10	1 (10%)	1 (10%)	1 (10%)	1	0	0	9	1	0	6	3
MFS	4	1 (25%)	1 (25%)	0 (0)	0	1	0	0	1	0	3	0
ATP	5	2 (40%)	2 (40%)	0 (0)	0	2	0	0	0	2	2	1
ENC	3	2 (67%)	0 (0)	2 (67%)	0	0	2	1	2	0	1	0
OMAS	2	0 (0)	0 (0)	0 (0)	0	0	0	0	0	0	1	0
MYEL	2	1 (50%)	1 (50%)	1 (50%)	1	0	0	0	1	0	1	0
ADEM	1	0 (0)	0 (0)	0 (0)	0	0	0	0	0	0	1	0
CTS	2	2 (100%)	2 (100%)	2 (100%)	2	0	0	0	2	0	0	0

		DENV positive		DENV IgM/DENV IgG				DENV IgM/ ZIKV or CHIV IgM or IgG			
	N	IGM	IgG	+/+	+/-	-/+	-/-	+/+	+/-	-/+	-/-
TOTAL	29	6 (20%)	24 (83%)	4	2	20	3	5	0	19	5
GBS	10	0 (0)	7 (70%)	0	0	7	3	0	0	7	3

MFS	4	1 (25%)	4 (100%)	1	0	3	0	1	0	4	0
ATP	5	0 (0)	5 (100%)	0	0	5	0	0	0	4	1
ENC	3	2 (67%)	2 (67%)	1	1	1	0	2	0	1	0
OMAS	2	0 (0)	2 (100%)	0	0	2	0	0	0	1	1
MYEL	2	2 (100%)	2 (100%)	2	0	0	0	2	0	0	0
ADEM	1	1 (100%)	1 (100%)	1	0	0	0	1	0	0	0
CTS	2	0 (0)	1 (50%)	0	0	1	1	0	0	2	0

Date ar n(%) or n. GBS = Guillain-Barré syndrome; MFS = Miller Fisher syndrome; ATP = Acute transient polyneuritis; ENC = encephalitis; OMAS = Opsoclonus myoclonus ataxia syndrome; MYEL = myelitis; ADEM = Acute demyelinating encephalomyelitis; CTS = Carpal tunnel syndrome

9. DISCUSSÃO

Entre os anos de 2015 e 2016 houve um crescente número de infecções por arbovírus sem precedentes. O ZIKV somente no ano de 2015 teve uma estimativa de 440.000-1.300.000 casos até o mês de fevereiro de 2016 (PLOURDE; BLOCH, 2016). No ano de 2016 (semana epidemiológica 52), todos estados brasileiros e distrito federal tiveram registro de casos de infecção pelo ZIKV, com o total de 2.015.319 (taxa de incidência de 105,3 casos/100 mil hab.). CHIKV e DENV também tiveram um alarmante número de casos no Brasil, com um total de 310.323 e 3.189.233 casos respectivamente entre os anos de 2015 e 2016 (BRASIL, 2017).

Registros de maiores números de casos concentraram-se no nordeste brasileiro. No estado da Bahia entre os anos de 2015 e 2016 houve um registro de 123.431 casos suspeitos de infecção pelo ZIKV, 77.450 por CHIKV e 119.673 por DENV. Durante o período supracitado, na Bahia também foram registrados aumento do número de complicações neurológicas provavelmente relacionadas às infecções pelos arbovírus circulantes, com 177 casos suspeitos de SGB ou outras complicações neurológicas em 2015 e 47 casos em 2016. Desde outubro de 2015 também se registram casos de síndrome congênita relacionada ao ZIKV (SC ZIKAV), outrora denominada de microcefalia, e até 2016, foram registrados 1.396 casos desta condição. (SECRETÁRIA DE SAÚDE DO ESTADO DA BAHIA, 2016).

Os dados apresentados nos diferentes artigos trouxeram a noção de que houve diversas doenças neurológicas associadas às arboviroses no período estudado. As doenças mais comumente descritas em outros estudos como a SGB e suas variantes foram predominantes nos nossos casos (14 de 29 – 48 %), porém diversas outras condições clínicas foram observadas, como a recentemente descrita polineuropatia sensitiva reversível (RSP), encefalites, mielites, ADEM e doenças mais raras como a SOMA.

Um grande número de variantes de SGB foram apresentadas no presente estudo: diplegia facial com parestesias, neuropatia atáxica aguda, síndrome de Miller Fisher. Esta observação é importante uma vez que durante os surtos de ZIKV, CHIKV e DENV os profissionais de saúde devem ficar alertas para apresentações atípicas dessa patologia.

A maioria dos pacientes admitidos com SGB clássica, apresentou no início do quadro doença mais grave, com escores clínicos com pontuações altas (HFS >3; HBS >4), entretanto quando estes pacientes foram reavaliados, todos tinham uma resolução quase completa da doença. A melhora clínica pode ter sido atribuída a um pronto tratamento já que o tempo médio entre o início da manifestação neurológica e início de infusão de imunoglobulina humana venosa (IVIG) foi de 9 dias, e entre a admissão hospitalar e IVIG foi de 3 dias. Outra possibilidade pode ser o curso da doença que parece ser mais benigno quando relacionado ao

ZIKV e outros arbovírus comparado à SGB secundária a outras doenças infecciosas (BAUD et al., 2017).

O padrão de ENMG dos pacientes com SGB do presente estudo foi de polineuropatia desmielinizante aguda (AIDP), o que confronta o padrão encontrado no estudo caso-controle conduzido na Polinésia Francesa (CAO-LORMEAU et al., 2016). Entretanto, o mesmo padrão de eletrodiagnóstico foi visto no estudo conduzido na Colômbia (ANAYA et al., 2017). O padrão desmielinizante de polineuropatia em SGB usualmente tem curso mais benigno quando comparado ao padrão de polineuropatia aguda axonal motora (AMAN), normalmente descrito relacionado a infecções pela bactéria *Campylobacter jejuni* (WAKERLEY; YUKI, 2015).

A maioria dos casos de SGB e suas variantes foram relacionadas a infecções prévias por ZIKV no presente estudo (78%), porém também foram observadas infecção recente por CHIKV (14%). Diversos casos de SGB já foram relacionados ao ZIKV e CHIKV previamente, porém a associação com DENV é mais rara (DO ROSARIO et al., 2016; PINHEIRO et al., 2016; PUCCIONI-SOHLER et al., 2017).

A presença de manifestações neurológicas leves relacionadas aos ZIKV foram descritas anteriormente. Nos casos clínicos publicados previamente, os pacientes apresentavam alterações sensitivas exclusivas, sem critérios de gravidade ou critérios clínicos para diagnóstico de SGB. Em alguns casos houve percepção de edema em nervos periféricos vistos por ultrassonografia (USG) porém a característica principal era o padrão de reversibilidade do quadro. Essa apresentação foi denominada pelos autores como polineurite transitória aguda ou polineuropatia sensitiva reversível (ATP/RSP) (MEDINA et al., 2016; NASCIMENTO et al., 2017). Foram descritos 5 casos no presente estudo, com características clínicas semelhantes e sem alterações nos exames laboratoriais ou eletrodiagnósticos. Foi observada a presença de infecção prévia pelo ZIKV em 2 casos e pelo CHIKV em outros 2 casos. Até o presente momento é a primeira descrição dessa manifestação neurológica relacionada ao CHIKV. Devido ao quadro benigno e a descrição limitada dessa alteração neurológica na literatura, diversos casos podem passar despercebidos durante os períodos de surtos de ZIKV ou CHIKV e o diagnóstico dessa síndrome pode ser subestimado (DO ROSARIO et al., 2018).

Outras manifestações neurológicas relacionadas ao ZIKV, DENV e CHIKV foram descritos previamente como a ADEM, mielites, encefalites, SOMA, alterações cognitivas dentre outras (CAROD-ARTAL et al., 2013; PINHEIRO et al., 2016).

A descrição da OMAS nos adultos, normalmente é relacionado a doenças infecciosas, porém assim como na população pediátrica, essa síndrome pode ser relacionada a manifestações paraneoplásica (BONNET; MEDEIROS DE BUSTOS; MOULIN, 2012). Foi descrito neste estudo o caso de uma paciente com quadro grave de alteração do estado mental, ataxia e

movimento anormal dos olhos, classificado como SOMA. Durante a investigação foram descartadas neoplasias e outras doenças infecciosas. Foi identificado através de RT-PCRq a presença do material genético do DENV-4 no soro e CHIKV no soro e do líquor. SOMA com evidência de infecção por DENV já foi descrita anteriormente, entretanto essa é a primeira descrição desta síndrome relacionada ao CHIKV e com evidência de coinfecção entre 2 diferentes arbovírus (TAN et al., 2014). Não há consenso sobre o tratamento dessa complicação neurológica, porém o uso de glicocorticoides e imunossupressores foram descritos na tentativa de resolução do quadro (DENNE et al., 2006; ROSTÁSY et al., 2006).

Diversas hipóteses são aventadas quando se discute a associação entre a infecção pelos arbovírus (atualmente DENV, CHIKV e ZIKV) e complicações neurológicas como SGB, encefalites, mielites, SOMA, dentre outras. Pesquisas com ZIKV mostram que o sistema nervoso humano, tanto em desenvolvimento quanto adulto, é suscetível a este vírus. A patogênese de SGB e de outras manifestações neurológicas imunomediada ainda é desconhecida, entretanto, mecanismos neuropatogênicos diretos, resposta imune hiperaguda, desregulação imune e mimetismo molecular contra antígenos do sistema nervoso são hipóteses previamente descritas (BAUD et al., 2017).

Coinfecção entre ZIKV, CHIKV e DENV vem sendo observado principalmente na América Latina, sendo a maioria das manifestações clínicas síndromes febris agudas ou doenças exantemáticas agudas (CHERABUDDI et al., 2016; VILLAMIL-GÓ MEZ et al., 2016; VILLAMIL-GÓMEZ et al., 2016; WAGGONER et al., 2016). Entretanto, já há descrição de encefalites, mielites, SGB, meningites e vasculites encefálicas em pacientes coinfectados (ACEVEDO et al., 2017). Grande parte dos pacientes descritos no presente estudo mostram positividade para mais de um dos arbovírus estudados, além da confirmação da presença de 2 diferentes vírus (DENV e CHIKV) por RT-PCRq em uma paciente com doença neurológica rara – SOMA. Esses dados trazem o alerta sobre a possibilidade de complicações mais graves quando os arbovírus se associam em coinfecção.

10. CONCLUSÕES

No presente estudo não só a GBS, que é a doença neurológica mais bem descrita em associação com ZIKV e CHIKV em adultos, mas várias outras manifestações clínicas foram observadas: encefalites, mielites, SOMA, polineurites e ADEM. Variações na apresentação clínica de GBS também foram frequentes nos pacientes estudados, trazendo o conhecimento de que há de se ficar atento a apresentações não usuais durante o período de surto de CHIKV, ZIKV e DENV. A presença de quadros mais benignos como a PTA/PSR também foi observada e deve ser inclusa no arsenal diagnóstico dos médicos que atendem pacientes em áreas de risco. Melhor conhecimento de formas mais benignas tem o potencial de identificar os pacientes que não necessitam de tratamento com IVIG ou plasmaférese, uma vez que tais opções terapêuticas têm custo financeiro elevado e devem ser reservadas para pacientes com quadro clínico mais grave.

Quartorze pacientes com GBS foram acompanhados no presente estudo, o que corresponde a 20% dos casos confirmados de GBS na Bahia no período entre os anos 2015 e 2016. Poucos estudos conseguiram avaliar a evolução dos pacientes com GBS após a alta hospitalar, por isso informações sobre o prognóstico desses pacientes é escassa. Notou-se uma recuperação funcional significativa nos pacientes acompanhados e reavaliados após 30 dias da alta hospitalar na nossa série de casos, com todos os avaliados apresentando independência funcional no período relatado. A melhora funcional pode ser atribuída a uma rapidez na implementação da terapia com IVIG ou característica da doença neurológica relacionada aos arbovírus.

A compreensão de que os arbovírus atualmente circulantes no Brasil podem desencadear complicações neurológicas de apresentações variadas, deve trazer aos profissionais que assistem as populações em áreas de risco de infecção por ZIKV, CHIKV e DENV uma maior capacidade em lidar e tratar dessas doenças. Esse conhecimento também deve trazer um alerta para os governantes e gestores dos serviços de saúde para promover ações de prevenção, combate ao vetor desses patógenos, além de melhor equipar hospitais e clínicas voltadas ao atendimento por essas infecções e complicações neurológicas.

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ANEXOS

Quadro 2 – Classificação da paralisia facial segundo o Sistema de House-Brackmann[13] (Academia Americana de Otorrinolaringologia).
Grau I: Normal Função facial normal em todas as áreas
Grau II: Disfunção Leve Geral: leve fraqueza notável apenas à inspeção próxima; pode haver sincinesia muito discreta No repouso: simetria e tônus normais Ao movimento: Testa: função boa a moderada Olho: fechamento completo com mínimo esforço Boca: leve assimetria
Grau III: Disfunção Moderada Geral: diferença óbvia, mas não desfigurante entre os dois lados; sincinesia e/ou espasmo hemifacial notável, mas não graves No repouso: simetria e tônus normais Ao movimento: Testa: movimento moderado a leve Olho: fechamento completo com esforço Boca: levemente fraca com o máximo esforço
Grau IV: Disfunção Moderadamente Importante Geral: fraqueza óbvia e/ou assimetria desfigurante No repouso: simetria e tônus normais Ao movimento: Testa: nenhum movimento Olho: fechamento incompleto Boca: assimetria com o máximo esforço
Grau V: Disfunção Importante Geral: apenas uma movimentação discretamente perceptível No repouso: assimetria Ao movimento: Testa: nenhum movimento Olho: fechamento incompleto Boca: movimento discreto
Grau VI: Paralisia Total Nenhum movimento

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APÊNDICES

APÊNDICE I

FICHA NEUROLOGIA - INTERNAMENTO

IDENTIFICAÇÃO

Nome:	Idade:	Data:
Início dos sintomas virose:	Início sint. Neurológicos	
Número no protocolo:	Viagem no último mês: 1. Sim 0. Não	
Sintomas semelhantes na família: 1. Sim 0. Não	Telefone:	
Endereço:		
Data Admissão	Data da alta	
Etnia: Branco	Negro	Pardo / Indigena

SINTOMAS VIROSE (0 Não; 1. sim; 9. Sem dados)

Rash cutâneo		Dor muscular		Prurido	
Artralgia (mono/oligo)		Dor de garganta		Edema mãos	
Artralgia (poli)		Conjuntivite		Edema pés	
Cefaleia		Astenia		Dispneia	
Febre		Parestesias de início?		Outros	

SINTOMAS NEUROLÓGICOS (0 Não; 1. sim; 9. Sem dados)

Fraqueza muscular		Sonolência		Alt. vesical		Queda da cabeça	
Paralisia facial uni		Confusão Mental		Dor lombar		Ataxia	
Paralisia facial bila		Disfagia		Disestesia			
House Brackmann		Disartria		Alt. marcha			
Diplopia		Afasia		Desequilíbrio			
Parestesias Mãos		Alt. campo visual		Convulsão			
Parestesias Pés		Alt. memória		Alt. intestinal			

EXAME NEUROLÓGICO D0

Humor: 1. Depressão, 2. Mania; 3. eutimia		Reflexos (0-4):					R. cut. abdominal: 1. presente; 0. aus.				
Alt. Nn. cranianos: 1. Sim 0. Não		Estilo-Radial:	D		E		FM: Deltoide	D		E	
Alt. Sensibilidade: 1. Sim 0. Não		Biccipital:	D		E		Biceps:	D		E	
Alt. coordenação: 1. Sim 0. Não		Tricipital:	D		E		Mãos:	D		E	
Alt. Força muscular: 1. Sim 0. Não		Patelar:	D		E		Elevação coxa:	D		E	
Alt. cognição: 1. Sim 0. Não		Aquileu:	D		E		Ext. perna:	D		E	
Alt. MOE: 1. Sim 0. Não		R. Cut. plantar:	D				Pés:	D		E	

DADOS LABORATORIAIS (0 negativo; 1. positivo; 9. Sem dados)

Sorologia Dengue: IgM		PCR Zika		PCR ChkV		Anti GQ1b	
Sorologia Dengue: IgG		Isolamento viral Zika		PCR Dengue		Anti GM1	
Sorologia ChkV: IgM		Sorologia Zika: IgM		Anti GD1b		Anti GT1b	
Sorologia ChkV: IgG		Sorologia Zika: IgG		Anti GM2		Anti GD1a	

ENMG__/__/___ (0 Não; 1. sim; 9. Sem dados)		ESTUDO DO LÍQUOR __/__/___	
Padrão desmielinizante		Proteinas	
Padrão axonal		glicose	
Padrão miopático		células	
Padrão radicular		Cels - diferencial	

DIAGNÓSTICO NEUROLÓGICO (0 Não; 1. sim; 9. Sem dados)

SGB clássico		Paraparética		Bickerstaff		Parestesias Isoladas	
Faringo-cervico-braquial		Diplegia facial+parestesias		Hipersonolência atáxica aguda		Alt. Intesitinal Isolada	
Fraqueza faringea		Miller fisher		Ptose Aguda			
ADEM		Neuropatia Atáxica Aguda		Midríase aguda			
Encefalite		Meningite		Oftalmoparesia aguda			

APÊNDICE I - CONTINUAÇÃO

FICHA NEUROLOGIA

TRATAMENTO AGUDO (0 Não; 1. sim; 9. Sem dados) [colocar datas de início ao lado]

Imunoglobulina + duração (dias		Amitriptilina	
Metilprednisolona + duração		IOT/VM + duração	
Plasmaferese + duração		Cateterismo vesical + duração	
Ciclofosfamida + duração		SNE + duração	
Prednisona oral		Internamento UTI/SEMI + duração	
Anticonvulsivantes		Dose adicional IVIG + duração	

PROGNÓSTICO(ESCALAS)			Doenças Prévias				
Rankin pré-TTO (D0)		Hughes D0		IAM	HAS	AVCh	
Rankin D3		Hughes D3		ICC	DM	Epileps.	
Rankin D5		Hughes D5		IRC	AVCi		

DETALHE EXAME SENSIBILIDADE D0 (0 ausente; 1. Diminuída; 2 normal; 9. Sem dados)

Palestesia Mão :	D		E		Dolorosa Mão :	D		E		Temperatura Joelho	D		E	
Palestesia pé :	D		E		Dolorosa pé :	D		E		Temper. cotovelo	D		E	
Palestesia joelho :	D		E		Dolorosa joelho :	D		E		Tato Mão :	D		E	
Palest. cotovelo :	D		E		Dolor. cotovelo :	D		E		Tato pés :	D		E	
Artrestesia Mão :	D		E		Temperatura Mão :	D		E		Tato Joelho	D		E	
Artrestesia pé :	D		E		Temperatura pés :	D		E		Tato cotovelo	D		E	
Nivel sensitivo? Local														

DETALHE EXAME SENSIBILIDADE D5 (0 ausente; 1. Diminuída; 2 normal; 9. Sem dados)

Palestesia Mão :	D		E		Dolorosa Mão :	D		E		Temperatura Joelho	D		E	
Palestesia pé :	D		E		Dolorosa pé :	D		E		Temper. cotovelo	D		E	
Palestesia joelho :	D		E		Dolorosa joelho :	D		E		Tato Mão :	D		E	
Palest. cotovelo :	D		E		Dolor. cotovelo :	D		E		Tato pés :	D		E	
Artrestesia Mão :	D		E		Temperatura Mão :	D		E		Tato Joelho	D		E	
Artrestesia pé :	D		E		Temperatura pés :	D		E		Tato cotovelo	D		E	
Nivel sensitivo? Local														

EXAME NEUROLÓGICO D5 (0 ausente; 1. Diminuída; 2 normal; 9. Sem dados)

Humor: 1. Depressão, 2. Mania; 3. eutimia		Reflexos (0-4):				R. cut. abdominal: 1. presente; 2. aus.			
Alt. Nn. cranianos: 1. Sim 2. Não		Estilo-Radial:	D		E	FM: Deltoide	D		E
Alt. Sensibilidade: 1. Sim 2. Não		Biccipital:	D		E	Biceps:	D		E
Alt. coordenação: 1. Sim 2. Não		Tricipital:	D		E	Mãos:	D		E
Alt. Força muscular: 1. Sim 2. Não		Patelar:	D		E	Elevação coxa:	D		E
Alt. cognição: 1. Sim 2. Não		Aquileu:	D		E	Ext. perna:	D		E
Alt. MOE: 1. Sim 2. Não		R. Cut. plantar:	D			Pés:	D		E

LINHA DE TEMPO

Virose __/__/__ a__/__/__ → Neuro __/__/__ a__/__/__ → coleta __/__/__ → TTO __/__/__ a__/__/__ → Reavaliação __/__/__ → Nova coleta __/__/__

Score	Classificação	Descrição
0	*Assintomático.*	Regressão dos sintomas.
1	*Sintomas sem incapacidade.*	Capaz de realizar suas tarefas e atividades habituais prévias.
2	*Incapacidade leve.*	Incapaz de realizar todas suas atividades habituais prévias, mas capaz de realizar suas necessidades pessoais sem ajuda.
3	*Incapacidade moderada.*	Requer alguma ajuda para as suas atividades, mas é capaz de andar sem ajuda de outra pessoa.
4	*Incapacidade moderada a grave.*	Incapacidade de andar sem ajuda, incapacidade de realizar suas atividades sem ajuda.
5	*Incapacidade grave.*	Limitada a cama, incontinência, requer cuidados de enfermeiros e atenção constante.
6	*Óbito.*	

Tabela 1. Escala de graduação do comprometimento neurológico (Hughes et al., modificada pelo Guillain-Barré Study Group[7]).

Grau	Características Clínicas
0	O paciente está saudável, sem nenhum sinal ou sintoma da SGB;
1	O paciente tem sinais ou sintomas menores e é capaz de correr;
2	O paciente é capaz de andar 5 metros através de um espaço aberto sem assistência, mas é incapaz de correr;
3	O paciente é capaz de andar 5 metros através de um espaço aberto com o auxílio de outra pessoa ou de muletas;
4	O paciente está restrito ao leito ou a cadeira de rodas;
5	O paciente necessita de ventilação assistida pelo menos uma parte do dia ou da noite;
6	Óbito.

APÊNDICE II

Hospital SANTA IZABEL

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

COMITÊ DE ÉTICA EM PESQUISA DO CENTRO DE PESQUISA GONÇALO MONIZ/FIOCRUZ:

Rua Waldemar Falcão, 121, Candeal, Salvador-Ba, CEP: 40296-710, Telefone: 3176-2285.

INSTITUIÇÕES PARTICIPANTES:

Clínica:

Setor de Neurologia do Hospital Santa Izabel
Praça Conselheiro Almeida Couto, 500 - Nazaré, Salvador - BA, 40050-410
Telefone:(71) 2203-8444. CNPJ 15153745000168/ CNES 0003832

Laboratório de Hematologia, Genética e Biologia Computacional (LHGB), Centro de Pesquisas Gonçalo Muniz, FIOCRUZ; Rua Waldemar Falcão, 121, Candeal, Salvador-Ba, CEP 40295-001.

PROJETO:

"Estudo da diversidade genética e história evolutiva do vírus chikungunya e outros arbovírus, no semiárido baiano e na região metropolitana da Salvador, e caracterização clínica/epidemiológica/hematológica dos indivíduos infectados."

PESQUISADORES RESPONSÁVEIS:

Luiz Carlos Júnior Alcântara; Telefone: 71-3176 2255/71-91031962

Mateus Santana do Rosário: Telefone: 71-99268682

Pedro Antonio Pereira de Jesus: Telefone: 71-91485803

Como voluntário o Sr (a) está sendo convidado a participar de uma pesquisa da Fundação Oswaldo Cruz (FIOCRUZ), localizada em Salvador da Bahia, que tem como o objetivo entender mais sobre os vírus Chikungunya, Zika e Dengue. Para isso, coletaremos um pouco de sangue dos pacientes com sintomas da febre do Chikungunya, Zika e Dengue que concordarem de participar deste estudo. Convido o Senhor (ou a Senhora) a participar deste estudo. Se concordar, nós solicitaremos a sua aprovação para

termos acesso aos seus dados clínicos e epidemiológicos constantes nos questionários que estão com os médicos e enfermeiras desta unidade de saúde (Hospital Santa Izabel). Também solicitaremos que nos doe 24 ml do seu sangue (três colheres de sobremesa), 10mL de urina e 3mL do líquido cefalorraquidiano (líquor).

Nós utilizaremos seu sangue, urina e líquor para ter o material genético dos vírus Chikungunya, Zika e Dengue para poder entender melhor a estrutura e função deste micróbios. Os resultado obtidos dará suporte para nós e outros cientistas podermos estudar novos possíveis métodos de tratamento e de diagnóstico. A sua participação neste estudo não trará benefícios diretos ao seu problema. Entretanto, o conhecimento obtido a partir desta pesquisa poderá contribuir para um melhor conhecimento em relação à infecção pelo Chikungunya, Zika e Dengue.

Informamos que o material (seu sangue, urina e líquor) que sobrar será inutilizado, seguindo todas as normas de biossegurança da Fiocruz Bahia.

O (a) Sr (a) poderá recusar-se a participar do estudo agora, ou em qualquer momento, sem que isto lhe traga qualquer constrangimento ou penalidade da instituição que está realizando este estudo.

A sua identidade será preservada e nenhum resultado obtido com esta pesquisa conterá o seu nome. Nós guardaremos os registros de cada indivíduo, em sala trancada, e somente o pesquisador responsável pela pesquisa e os médicos trabalhando na equipe terão acesso a estas informações. Cada indivíduo receberá um número para ser utilizado no laboratório. Se qualquer relatório ou publicação resultar deste trabalho, a identificação do paciente não será revelada, e confirmo que a seguinte informação constará nos artigos publicados: "Agradecemos a todos os pacientes que participaram desta pesquisa". Os Resultados serão relatados de forma sumarizada e o indivíduo não será identificado.

O risco associado à coleta de sangue poderá ser de um pequeno desconforto no local, a um possível sangramento e hematomas (um pequeno acúmulo de sangue). Não há risco associado á coleta de urina.

No caso de ocorrência de problemas médicos durante a coleta, você terá o auxílio de um dos médicos desta unidade, que participa deste projeto e estará presente durante todas as coletas, sem ônus algum.

Os pesquisadores responsáveis por este projeto estarão à disposição, em qualquer momento, para esclarecer alguma dúvida ou questão que o Sr (a) tenha em relação a este estudo.

Hospital
SANTA IZABEL

Se concordar em participar, por favor, assine abaixo.

Declaro que li este consentimento e que de livre e espontânea vontade, concordei em participar desta pesquisa.

Salvador, Ba, _____/_____/_____

Nome:_____

Assinatura:_____

Impressão datiloscópica :

COMPROMISSO DO INVESTIGADOR

Eu discuti as questões acima apresentadas com os indivíduos participantes no estudo ou com o seu representante legalmente autorizado. É minha opinião que o indivíduo entende os riscos, benefícios e obrigações relacionadas a este projeto.

Salvador-BA, _____ de _____ de _____.

Assinatura do Pesquisador responsável:_____

Dados do Pesquisador Responsável:

Nome: Dr. Luiz Carlos Junior Alcântara

Residente na Rua Cícero Simões 225, apto 301, Pituba, Salvador, Bahia.

Telefones: (71) 3176-2255 ou (71) 9103-1962