Molecular Mimicry between Zika virus and central nervous system inflammatory demyelinating disorders: the role of NS5 Zika virus epitope and PLP autoantigens

Laise Carolina França
Federal University of Rio de Janeiro State
Fabrícia Lima Fontes-Dantas
Federal University of Rio de Janeiro State
Diogo Gomes Garcia
Federal University of Rio de Janeiro State
Amanda Dutra de Araújo
Federal University of Rio de Janeiro State
João Paulo da Costa Gonçalves
Universidade Federal do Rio de Janeiro Instituto de Puericultura e Pediatria Martagao Gesteira
Cláudia Cecília da Silva Rêgo
Federal University of Rio de Janeiro State
Elielson Veloso da Silva
Federal University of Rio de Janeiro State
Osvaldo José Moreira do Nascimento
Federal University of Rio de Janeiro State
Fernanda Cristina Rueda Lopes
Universidade Federal Fluminense
Alice Laschuk Herlinger
Universidade Federal do Rio de Janeiro
Renato Santana de Aguiar
Universidade Federal do Rio de janeiro
Orlando da Costa Ferreira Junior
Universidade Federal do Rio de Janeiro
Fernando Faria Andrade Figueira
Hospital da Ordem da Penitência
Jorge Paes Barreto Marcondes de Souza
Universidade Federal do Rio de Janeiro Instituto de Puericultura e Pediatria Martagao Gesteira
Joelma Freire De Mesquita
Federal University of Rio de Janeiro State

Soniza Vieira Vieira Alves-Leon (sonizavieiraalvesleon@gmail.com)
Universidade Federal do Estado do Rio de Janeiro https://orcid.org/0000-0002-1538-6730

Research article

Keywords: Zika virus, inflammatory demyelination disorders, molecular mimicry NS5, PLP

Posted Date: February 4th, 2020

DOI: https://doi.org/10.21203/rs.2.22564/v1

Abstract

Background: Evidences indicate a strong link between Zika virus (ZikV) and neurological complications. Acute myelitis, optic neuritis, polyneuropathy and encephalomyelitis that mimic inflammatory idiopathic demyelination disorders (IIDD) after ZikV infection have been reported in Brazil. In that context, the present study aims to investigate the possible occurrence of molecular mimicry between ZikV antigens and Multiple Sclerosis (MS) autoantigens, the most frequent IIDD of the central nervous system (CNS).

Methods: A retrospective cohort study with 305 patients admitted due to suspected arbovirus infection in Rio de Janeiro was performed, all subjects were submitted to neurological examination and biological sample was collected for serologic and molecular diagnostic. Bioinformatics tools were used to analyze the peptides shared between ZikV antigens and MS autoantigens.

Results: Of 305 patients, twenty-six were positive for ZikV and 4 presented IDD pattern found in MS cases. Sequence homology comparisons by bioinformatics approach between NS5 ZikV (most common strains) and PLP MS protein revealed a homology of 5/6 consecutive amino acids (CSSVPV/CSAVPV) with 83% identity, deducing a molecular mimicry. In addition, analysis of the 3D structures of both proteins revealed a similar conformation with alpha helix presentation.

Conclusions: Molecular mimicry between NS5 Zika virus antigen and PLP MS autoantigens emerge as a possible mechanism for IDD spectrum in genetically susceptible individuals.

Background

Over 80% of Zika Virus (ZikV) infections in humans are asymptomatic. Typical symptoms can include rash, fever, joint pain and conjunctivitis for a period of 7 days (1). The outbreak of ZikV has increased the occurrence of long term neurological complications (2). In addition, ZikV was detected by serology in cerebrospinal fluid (CSF), molecular and histopathological analysis of the brain and amniotic fluid of microcephalic fetuses (3,4). ZikV has also been associated to central nervous system (CNS) inflammatory demyelinating disorders (IDD) including optic neuritis (5), neuromyelitis optica spectrum disorders (NMOSD) (6), transverse myelitis and acute disseminated encephalomyelitis (ADEM) (3). Our group has recently published a case in which the coexistence of the virus in the CNS of an MS patient led to the development of an ADEM-like episode (7).

Besides its direct neurotropic effect (8), it is believed that ZikV may function as a trigger leading to the development of an immune-mediated injury against many parts of the CNS (9). ZikV has already been related to the development of several autoimmune conditions (10). In Guillain-Barre syndrome (GBS), for example, the molecular mimicry between glycolipids and surface molecules of the virus has explained the majority of cases (11). Interestingly, ZikV is commonly associated with magnetic resonance imaging (MRI) lesions distributed in space and time, regarding heterogeneous gadolinium enhancement, as seen in the MS criteria (12). Moreover, serum positivity for autoantibodies against myelin oligodendrocyte glycoprotein (MOG), a specific antibody against the myelin sheath was recently associated with ZikV

(13). As many radiological and clinical aspects of ZikV infection may mimic IIDD, patients can be misdiagnosed. MS is the most frequent IIDD of the CNS (14), and several evidences have shown that molecular mimicry is a possible epigenetic mechanism in genetically susceptible individuals (15).

To investigate the mechanisms of ZikV induced neurological manifestations, it is essential to use various reproducible *in vitro* models and bioinformatics tools capable of recapitulating complex neurodevelopmental disorders, in an attempt to find specific targets. The molecular mechanisms underlying these conditions in adults are not clear. Focusing on the MS-like pattern, the present study investigated the possible occurrence of molecular mimicry between ZikV antigens and MS autoantigens. The underlying rationale is that shared peptides between pathogen and human host may lead to a break in immune tolerance through a cross-reactivity phenomenon (16).

Methods

Study population and biological samples

A retrospective cohort study was performed with patients admitted in three university hospitals and referred by Laboratório Central Noel Nutels (LACEN) in Rio de Janeiro. This work was approved by the National Council for Ethics in Research (CAAE 69411317.6.0000.5258). All subjects signed an informed consent agreeing to participate in this research. From 2016 to 2019, 305 patients with suspected arbovirus infection were evaluated by a multidisciplinary team. Complete physical and neurological examination was performed and, when necessary, MRI was requested. Biological sample (blood, urine, and CSF) was collected on admission and, according to clinical indication, tested by serology and/or ZikV molecular diagnostic.

Sequence analysis

Peptide sharing between ZikV antigens and MS autoantigens was analyzed as follow: A viral polyprotein library was constructed using the major viral antigens reported in the literature and protein sequences available in NCBI Protein Reference Sequences (https://www.ncbi.nlm.nih.gov/protein). A MS autoantigen library was constructed at random through UniProtKB Database (www.uniprot.org/) using ‘Multiple Sclerosis’ as a keyword. The result was filtered and only the proteins confirmed as autoantigens were collected. ZikV polyproteins and MS autoantigens identified are outlined in Table S1. The two libraries were analyzed for matches using BLASTP (https://blast.ncbi.nlm.nih.gov/Blast.cgi) and sequence alignment was done using EMBOSS (https://www.ebi.ac.uk/Tools/psa/emboss_water/).

Antigenic prediction

To confirm whether the NS5 ZikV sequence studied has antigenic properties, VaxiJen version 2.0 (http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html) was used. A threshold antigenic score of

0.5 was defined in order to filter probable non-antigenic sequences. Vaxijen server performs alignment-independent prediction, which is based on auto cross covariance (ACC) transformation of protein sequences into uniform vectors of principal amino acid properties.

3D Comparative modelling

The 3D models were built using the Swiss-Model, an online modeling server (https://swissmodel.expasy.org/). The template modeling scores (TM-scores) and root mean square deviations (RMSDs) of the NS5 ZIKV and PLP MS three-dimensional overlap were calculated using TM-Align.

Results

Inflammatory demyelinating disorder phenotypes in patients with ZikV infection

A total of 305 patients were evaluated. 26 were positive for ZikV and the remaining were diagnosed with either Dengue or Chikungunya. Out of the ZikV positive patients, 4 were classified as having IDD of the CNS requiring differential diagnosis with MS. Clinical examination, imaging, electrophysiologic, and laboratory findings of these patients are exposed in Table 1 and Figure 1–4.

Sequence sharing between ZIKV polyproteins and MS autoantigens

The bioinformatics approach identified an 83% identity between the NS5 antigen of ZikV and PLP MS autoantigen, deducing the molecular mimicry among them. The obtained alignment between the peptide sequences is represented in Figure 5A. Although statistically non-significant, it was also possible to observe a 67% identity between NS3 antigen of ZikV and MOG MS autoantigen. The identity results between all sequences are depicted in Table S2. In addition, sequence analysis of NS5 using VaxiJen version 2.0 resulted in a score of 0.5091, confirming the antigenicity of the sequence studied.

Structural conformation between NS5 ZIKV and PLP MS

In order to predict the 3D structures conformation of the two proteins, TM-Align was used to align them. As BlastP showed us a high identity between a particular region of PLP and NS5, a structural conformation was performed only with that region where the corresponding high identity was obtained $PLP^{131-198}$ and $NS5^{281-325}$ (Figure 5B). The CSAVPV sequence which is 86% identity by BlastP, obtained a TM-score of 0.47071 and RMDS of 2.39 and is in alpha helix structure of both proteins.

Discussion

Several studies have shown that IDD in CNS can be triggered by viral infection or immunizations. After a variable period of incubation, myelin destruction undergoes courses of remission and exacerbation. MS is a most common disease that compromises CNS myelin sheath (17).

Viral infection can trigger autoimmune diseases through different mechanisms: molecular mimicry, epitope spreading, bystander activation, superantigen production, and inadequate activation of immune response (18). Molecular mimicry can be defined as similar structures shared by a host epitope and microorganism or environmental proteins (18). Using bioinformatics tools, common sequences and structural homology between Chikungunya virus (ChikV) E1 glycoprotein and human HLA-B27 molecule were identified. In addition, the peptides derived from ChikV glycoprotein E1 induced significant inflammation in C57BL/6J mice (19). Based on proteomic studies and sequence analysis, some evidence has also shown that Dengue Hemorrhagic Fever may be caused by molecular mimicry between different coagulation molecules with prM, E and NS1 viral proteins (20). Furthermore, it is already widely proposed that cross-recognition of common viral peptides with myelin antigens induces a molecular mimicry involved in MS development, especially in genetically susceptible individuals (15).

Zika fever is a self-limited disease, still, less than 5% of symptomatic patients may develop neurological manifestations (21,22). We evaluated 305 patients who had suspected infection with common arboviruses circulating in Brazil, of which 26 were positive for ZikV and, surprisingly, 4 patients had MS-like multifocal syndromes.

Patient 1 presented with headache, optical neuritis, and cervical myelitis associated to a cervical lesion (Figure 1 E) and asymptomatic multifocal brain lesions on MRI, one of which had gadolinium enhancement. This distribution of brain lesions, paired with positive oligoclonal bands (OCB) found on CSF analysis, resembles the pattern usually found in MS (Figure 1 A-D and Table 1). Although this patient developed these neurological manifestations five days after the first symptoms of viral infection, it was only possible to make the ZikV diagnosis after sixty days, thus explaining the IgM negativity in serum. Patient 2 had a diagnosis of acute flaccid paraplegia 11 days after a viral prodrome, and 3 months later developed tetraparesis associated with longitudinal extensive transverse myelitis (Figure 2 C and D), centrally located (Figure 2 C3, D3), with focal tapering of the cervical/dorsal transition on sagittal STIR (Figure 2 C1), resembling the extension and sequelae areas usually seen in NMOSD. Furthermore, the lesion had anterior horn involvement (Figure 2 D4). A recent case report identified concurrent GBS and ADEM in a 24-year-old woman who developed acute ZikV infection. The authors postulate this case was para-infectious, induced by neurotropism and activation of an immune response against ZikV (23). This same mechanism is probably involved in the development of this NMOSD phenotype in our patient. Patient 3 presented with tetra paresis and ataxia associated to brain lesions mainly affecting the brainstem on axial T2 images, including the posterior aspect of the mesencephalon (Figure 3 E), pons (Figure 3 F) and the medial cerebellar peduncle (Figure 3 G). Patient 4 presented with optic neuritis and multifocal myelitis with cervical and dorsal lesions, as usually found in a first manifestation of MS

(Figure 4 A, B). This patient could be classified as having a clinical isolated syndrome (CIS) with high risk of conversion to MS due the distribution and number of T2 white matter lesions. Although the optical neuritis pattern resembles the one of NMOSD, the spinal cord lesions are MS-like.

Lucchese *et al,* 2016, observed that ZikV antigens are commonly involved in microcephaly and GBS. 129 immunopositive epitopes are reported as having peptide overlap with human proteins that may relate to demyelination and axonal neuropathies. This indicates that cross-reactivity with human proteins might contribute to the mechanisms linking ZikV infection to GBS (11). The IDD phenotype attributed to ZikV infection seems to mimic MS manifestations. Molecular mimicry is assessed in this study by investigating homologous regions between ZikV antigens and human MS autoantigens using bioinformatics tools. Sequence homology comparisons between NS5 ZikV and PLP MS protein revealed a homology of 5/6 consecutive amino acids CSSVPV/CSAVPV (Figure 5A). A study that performed antigenic B-cell epitopes prediction found an antigenic peptide from position 528 to 539 (NAI*CSSVPV*DWV) of ZIKV NS5, which had the maximum residual score of 1.203 and might present a preliminary set of peptides for future vaccine development against ZIKV (24). Calculating the TM-score of NS5 ZIKV and PLP MS 3D structures demonstrated that both proteins are in almost the same fold, both are in alpha helix and they have topological similarity (Figure 5B) (25).

Interestingly, ZIKV African (MR766) lineage strain, revealed exactly the same Human PLP sequence (CSAVPV), and recombinant NS5 proteins from Africa and from Brazil revealed similar levels of RNA synthesis (26). It is already known that MR766 strain is more virulent and causes more severe brain damage than current Asian lineage and dengue virus (27). When inoculated subcutaneously in adult transgenic mice (knockout) C57BL/6 $Stat2^{-/-}$, MR766 strain induces short episodes of severe neurological symptoms, followed by lethality. Furthermore, this strain was able to induce higher levels of inflammatory cytokines and markers associated with cellular infiltration into the brain of infected mice (28). Li *et al,* 2019, observed that MR766 strain and epidemic Brazilian (BR15 and ICD) ZIKV strains are different in viral attachment to host neuronal cells, viral permissiveness and replication, as well as in the induction of cytopathic effects (29).

Autoreactivity to PLP in patients with MS has been investigated in human and animal model by various groups worldwide (30). A recent study involving PLP's Epitopes involved in MS, found CSAVPV (in $PLP^{161-177}$ residues) among the most immunogenic regions of PLP (31). In addition, the crystal structure of the NS5 ZikV protein reveals a conserved domain conformation of Flaviviruses, a genus that includes a variety of human pathogens such as dengue virus, yellow fever virus, West Nile virus, Spondweni virus and the Japanese encephalitis virus (32). So, the presence of high identity between NS5 ZikV and PLP, an autoantigen widely implicated in the pathogenesis of MS (33), leads us to postulate that molecular mimicry may have a role in the development of inflammatory demyelinating damage, a hallmark of the IDD produced by this genus of virus.

Both genetic and environmental factors have been shown to contribute to the pathogenesis of autoimmune diseases. It is well-established that *HLA-DR15* haplotype bears the strongest association to

MS (34). In a Brazilian study, it was observed that the presence of *HLA-DRB1**1501 allele confers an ethnicity-dependent MS susceptibility in Caucasian patients and that *HLA-DQB1**0602 allele confers an ethnicity independent susceptibility (35). Using HLA class II transgenic (Tg) mice, several studies have demonstrated HLA-DR-dependent disease following immunization by MBP, PLP, or MOG (36,37). However, it was observed that *HLA-DRB1**1501 Tg mice were refractory to disease induction by overlapping PLP peptides, while *HLA-DQB1**0602 Tg mice were susceptible to disease induction by $PLP^{139–151}$ and $PLP^{175–194}$ peptides (38). It has been seen that Both $PLP^{139–151}$ and $PLP^{178–191}$ epitopes are key targets of T-cells, and are increased in MS patients versus healthy controls (39). However, this does not mean that $PLP^{161–177}$ residues are not encephalitogenic-related, but that they need further animal and human model studies. Therefore, PLP autoimmunity and HLA haplotype have been strongly associated with lesion localization, as well as remission and relapse rates in MS (40).

Conclusion

The concept of molecular mimicry remains a viable hypothesis for understanding the genetics, epigenetics, and environmental involvement in the pathogenic mechanisms of IDD. Studies using bioinformatics tools further encourage the identification of molecules that could be used in the development of either diagnostic or prognostic biomarkers. We found that NS5 ZikV presented a high identity with PLP MS autoantigen and both are structurally similar with alpha helix chains. These findings may justify IDD CNS manifestations following ZikV infection, as in the 4 cases here reported. Further investigation is required to understand whether $PLP^{161–177}$ residues are encephalitogenic and how the recognition of NS5 epitopes by HLA molecules drives the pathogenic T-cell autoimmune response *in vivo.*

List Of Abbreviations

ACC: Auto Cross Covariance

ADEM: Acute Disseminated Encephalomyelitis

BLASTP: Basic Local Alignment Search Tool for Protein

BR15: Brazilian Zika Virus strain

C57BL/6J: A Common Inbred Strain of Laboratory Mouse—Substrain 6J

CAAE: Certificado de Apresentação para Apreciação Ética

ChiKV: Chikungunya Virus

CIS: Clinical Isolated Syndrome

CNS: Central Nervous System

CSF: Cerebrospinal Fluid

EMBOSS: European Molecular Biology Open Software Suite

FLAIR: Fluid Attenuated Inversion Recovery

GBS: Guillain-Barre Syndrome

HLA: Human Leukocyte Antigen

ICD: Brazilian Zika Virus Strain

IDD: Inflammatory Demyelination Disorders

IgG: Immunoglobulin G

IgM: Immunoglobulin M

LACEN: Laboratório Central Noel Nutels

MOG: Myelin Oligodendrocyte Glycoprotein

MR 766: African Zika Virus Strain

MRI: Magnetic Resonance Imaging

MS: Multiple Sclerosis

NCBI: National Center for Biotechnology Information

NMOSD: Neuromyelitis Optica Spectrum Disorders

NS1, 3 or 5: Non Structural Protein 1, 3 or 5

OCB: Oligoclonal Bands

PLP: Myelin proteolipid protein

RNA: Ribonucleic Acid

RT-PCR: Reverse Transcription Polymerase Chain Reaction

STIR: Short Tau Inversion Recovery

Tg: Transgenic

ZikV: Zika Virus

Declarations

Ethics approval and consent to participate

This work was approved by the National Council for Ethics in Research (CAAE 69411317.6.0000.5258) from Universidade Federal do Estado do Rio de Janeiro (supplementary material 1). All subjects signed an informed consent agreeing to participate in this research.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary 2 information files.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Brazilian National Council for Scientific and Technological Development (CNPq Number 440779/2016-2), support reagents and equipment to the laboratory, Coordination for the Improvement of Higher Education Personnel (CAPES Number 88887.130752/2016-00) support fellowship grant to the MSC. and PhD students, and also support grant to the Post PHD researchers, Department of Science and Technology (DECIT No. 14/2016) and Rede Nacional de Especialistas em ZIKA e Doenças Correlatas (RENEZIKA) support the equipment for the laboratory, and Foundation for Rio de Janeiro State Research (FAPERJ) support the reagents and administrative needs.

Authors' contributions

SVAL and FLFD conceived and designed the experiments. SVAL, FLFD, LCF, DGG, ADA, JPCG, CCSR, EVS, OJMN, FCRL, FFAF and JPBMS participated in subject recruitment and collection of the samples. ALH, RSA, OCFJ performed serology and molecular diagnostic. FLFD, LCF and JFM performed bioinformatics analyzes. LCF, FLFD and SVAL analyzed the data and drafted the manuscript. All authors read and approved the final version.

Acknowledgements

We appreciate the support of Secretaria de Saúde do Estado do Rio de Janeiro and Laboratório Central Noel Nutels (LACEN) and the Laboratorio de Virologia Molecular of Professor Amilcar Tanuri.

References

1. Baud D, Gubler DJ, Schaub B, Lanteri MC, Musso D. An update on Zika virus infection. Lancet [Internet]. 2017 Nov 4;390(10107):2099–2109 Available from: https://doi.org/10.1016/S0140–6736(17)31450–2
2. Lannuzel A, Ferge J-L, Lobjois Q, Signate A, Roze B, Tressieres B, et al. Long-term outcome in neuroZika: When biological diagnosis matters. Neurology. 2019 May 21;92(21):e2406-e2420. Available from: https://doi.org/10.1212/WNL.0000000000007536
3. Galliez RM, Spitz M, Rafful PP, Cagy M, Escosteguy C, Germano CSB, et al. Zika virus causing encephalomyelitis associated with immunoactivation. Open Forum Infect Dis. 2016; 3(4):3–6 Available from: https://doi.org/10.1093/ofid/ofw203
4. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. N Engl J Med [Internet]. 2016; 374(10):951–8. Available from: https://doi.org/10.1056/NEJMoa1600651.
5. Barrier B. Ocular Manifestations of Emerging Flaviviruses and the Blood-Retinal Barrier. Viruses. 2018;10(530):1–20. Available from: https://doi.org/10.3390/v10100530.
6. Aspahan MC, Leonhard SE, Gomez RS, Rocha E da S, Vilela MR da S, Alvarenga PPM, et al. Neuromyelitis optica spectrum disorder associated with Zika virus infection. Vol. 9, Neurology. Clinical practice. United States;. 2019.p.e1–3; Available from: https://doi.org/10.1212/CPJ.0000000000000546.
7. Alves-Leon SV, Lima M da R, Nunes PCG, Chimelli LMC, Rabelo K, Nogueira RMR, et al. Zika virus found in brain tissue of a multiple sclerosis patient undergoing an acute disseminated encephalomyelitis-like episode. Mult Scler. 2018;Mar;25(3):427–430. Available from: https://doi.org/10.1177/1352458518781992.
8. Platt DJ, Smith AM, Arora N, Diamond MS, Coyne CB, Miner JJ. Zika virus–related neurotropic flaviviruses infect human placental explants and cause fetal demise in mice. Sci Transl Med [Internet]. 2018; Jan 31;10(426) Available from: https://doi.org/10.1126/scitranslmed.aao7090
9. Wen J, Shresta S. T Cell Immunity to Zika and Dengue Viral Infections. J Interf Cytokine Res [Internet]. 2017; Nov 1;37(11):475–9 Available from: https://doi.org/10.1089/jir.2017.0106
10. Monsalve DM, Pacheco Y, Acosta-ampudia Y, Rodríguez Y, Ramírez-santana C. Zika virus and autoimmunity. One-step forward. Autoimmun Rev [Internet]. 2017;17(S1568–9972):30258–6 Available from: https://doi.org/10.1016/j.autrev.2017.10.008
11. Lucchese G, Kanduc D. Zika virus and autoimmunity: From microcephaly to Guillain-Barré syndrome, and beyond. Autoimmun Rev [Internet]. 2016; 15(8):801–8. Available from: https://doi.org/10.1016/j.autrev.2016.03.020
12. Zare M, Elham M, Andrea K. Neuroimaging findings of Zika virus infection : a review article. Jpn J Radiol. 2016; 34(12):765–70. Available from: https://doi.org/10.1007/s11604–016–0588–5.

13. Neri VC, Xavier MF, Barros PO, Melo Bento C, Marignier R, Papais Alvarenga R. Case Report: Acute Transverse Myelitis after Zika Virus Infection. Am J Trop Med Hyg. 2018; Dec;99(6):1419–1421. Available from: https://doi.org/10.4269/ajtmh.17–0938
14. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet [Internet]. 2018; 6736(18):1–15 Available from: https://doi.org/10.1016/S0140–6736(18)30481–1
15. Huynh JL, Casaccia P. Epigenetic mechanisms in multiple sclerosis: impications for pathogenesis and treatment. Lancet Neurol. 2013; 12(2):195–206. Available from: https://doi.org/10.1016/S1474–4422(12)70309–5.
16. Robinson AP, Harp CT, Noronha A, Miller SD. The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment. Handb Clin Neurol. 2014; 122:173–89. Available from: https://doi.org/10.1016/B978–0–444–52001–2.00008-X.
17. Waubant E, Ponsonby a L, Pugliatti M, Hanwell H, Mowry EM, Hintzen RQ. Environmental and genetic factors in pediatric inflammatory demyelinating diseases. Neurology. 2016; 87(9 Suppl. 2):S20–7. Available from: https://doi.org/10.1212/WNL.0000000000003029.
18. Oldstone MB. Molecular mimicry and immune-mediated diseases. FASEB J Off Publ Fed Am Soc Exp Biol. 1998 Oct;12(13):1255–65. Available from: https://doi.org/ 10.1096/fasebj.12.13.1255.
19. Reddy V, Desai A, Krishna SS, Vasanthapuram R. Molecular Mimicry between Chikungunya Virus and Host Components: A Possible Mechanism for the Arthritic Manifestations. PLoS Negl Trop Dis. 2017;11(1):1–20. Available from: https://doi.org/10.1371/journal.pntd.0005238
20. Lin Y-S, Yeh T-M, Lin C-F, Wan S-W, Chuang Y-C, Hsu T-K, et al. Molecular mimicry between virus and host and its implications for dengue disease pathogenesis. Exp Biol Med (Maywood). 2011 May;236(5):515–23. Available from: https://doi.org/10.1258/ebm.2011.010339
21. Meltzer E, Leshem E, Lustig Y, Gottesman G, Schwartz E. The Clinical Spectrum of Zika Virus in Returning Travelers. Am J Med [Internet]. 2016;129(10):1126–30. Available from: https://doi.org/10.1016/j.amjmed.2016.04.034
22. Beckham JD, Pastula DM, Massey A, Tyler KL. Zika virus as an emerging global pathogen: Neurological complications of zika virus. JAMA Neurol. 2016;73(7):875–9. Available from: https://doi.org/10.1001/jamaneurol.2016.0800
23. Román GC, Anaya J-M, Mancera-Páez Ó, Pardo-Turriago R, Rodríguez Y. Concurrent Guillain-Barré syndrome, transverse myelitis and encephalitis post-Zika: A case report and review of the pathogenic role of multiple arboviral immunity. J Neurol Sci [Internet]. 2019 Jan 15;396:84–5. Available from: https://doi.org/10.1016/j.jns.2018.10.032
24. Mirza MU, Rafi S, Ali A, Munir M, Ikram N, Manan A, et al. Towards peptide vaccines against Zika virus : Immunoinformatics combined with molecular dynamics simulations to predict antigenic epitopes of Zika viral proteins. Nature. 2016(July):1–18. Available from: https://doi.org/10.1038/srep37313
25. Zhang Y, Skolnick J. TM-align: a protein structure alignment algorithm based on the TM-score. Nucleic Acids Res. 2005;33(7):2302–9. Available from: https://doi.org/10.1093/nar/gki524

26. Zhao B, Yi G, Du F, Chuang YC, Vaughan RC, Sankaran B, et al. Structure and function of the Zika virus full-length NS5 protein. Nat Commun [Internet]. 2017;8:1–9. Available from: http://dx.doi.org/10.1038/ncomms14762
27. Shao Q, Herrlinger S, Zhu Y-N, Yang M, Goodfellow F, Stice SL, et al. The African Zika virus MR–766 is more virulent and causes more severe brain damage than current Asian lineage and dengue virus. Development [Internet]. 2017/10/09. 2017 Nov 15;144(22):4114–24. Available from: https://doi.org/10.1242/dev.156752
28. Tripathi S, Balasubramaniam VRMT, Brown JA, Mena I, Grant A, Bardina S V, et al. A novel Zika virus mouse model reveals strain specific differences in virus pathogenesis and host inflammatory immune responses. Plos. 2017;1–19. Available from: https://doi.org/10.1371/journal.ppat.1006258
29. Infection EZV, Li G, Bos S, Tsetsarkin KA, Pletnev AG, Despr P, et al. The Roles of prM-E Proteins in Historical and Epidemic Zika Virus-Mediated Infection and Neurocytotoxicity. Viruses MDPI. 2019 Feb; 11(2): 157. Available from: https://doi.org/10.3390/v11020157
30. Greer JM. Autoimmune T-Cell Reactivity to Myelin Proteolipids and Glycolipids in Multiple Sclerosis. Mult Scler Int. 2013; 2013: 151427. Available from: https://doi.org/10.1155/2013/151427
31. Zamanzadeh Z, Ataei M, Nabavi SM, Ahangari G, Sadeghi M. In Silico Perspectives on the Prediction of the PLP ' s Epitopes involved in Multiple Sclerosis. Natl Inst Genet Eng Biotechnol [Internet]. 2017;15(1):10–21. Available from: http://dx.doi.org/10.15171/ijb.1356
32. Wang B, Tan XF, Thurmond S, Zhang ZM, Lin A, Hai R, et al. The structure of Zika virus NS5 reveals a conserved domain conformation. Nat Commun [Internet]. 2017;8:1–6. Available from: http://dx.doi.org/10.1038/ncomms14763
33. Kuhlmann T, Ludwin S, Prat A, Antel J, Bruck W, Lassmann H. An updated histological classification system for multiple sclerosis lesions. Acta Neuropathol. 2017 Jan;133(1):13–24.
34. Svejgaard A. The immunogenetics of multiple sclerosis. Immunogenetics. 2008;60(6):275–86. Available from: http://doi.org/10.1007/s00251–008–0295–1
35. Alves-Leon S V, Papais-Alvarenga R, Magalhaes M, Alvarenga M, Thuler LCS, Fernandez y Fernandez O. Ethnicity-dependent association of HLA DRB1-DQA1-DQB1 alleles in Brazilian multiple sclerosis patients. Acta Neurol Scand. 2007 May;115(5):306–11. Available from: http://doi.org/10.1111/j.1600–0404.2006.00750.x
36. Mangalam AK, Khare M, Krco C, Rodriguez M, David C. Identification of T cell epitopes on human proteolipid protein and induction of experimental autoimmune encephalomyelitis in HLA class II-transgenic mice. Eur J Immunol. 2004 Jan;34(1):280–90. Available from: http://doi.org/10.1002/eji.200324597
37. Rich C, Link JM, Zamora A, Jacobsen H, Meza-Romero R, Offner H, et al. Myelin oligodendrocyte glycoprotein–35–55 peptide induces severe chronic experimental autoimmune encephalomyelitis in HLA-DR2-transgenic mice. Eur J Immunol. 2004 May;34(5):1251–61. Available from: http://doi.org/10.1002/eji.200324354

38. Kaushansky N, Altmann DM, David CS, Lassmann H, Ben-nun A. DQB1 * 0602 rather than DRB1 * 1501 confers susceptibility to multiple sclerosis-like disease induced by proteolipid protein (PLP). J Neuroinflammation [Internet]. 2012;9(1):29. Available from: http://doi.org/10.1186/1742–2094–9–29
39. Bielekova B, Sung M-H, Kadom N, Simon R, McFarland H, Martin R. Expansion and functional relevance of high-avidity myelin-specific CD4+ T cells in multiple sclerosis. J Immunol. 2004 Mar;172(6):3893–904. Available from: http://doi.org/10.4049/jimmunol.172.6.3893
40. Greer JM, Csurhes PA, Muller DM, Pender MP. Correlation of blood T cell and antibody reactivity to myelin proteins with HLA type and lesion localization in multiple sclerosis. J Immunol. 2008 May;180(9):6402–10. Available from: http://doi.org/10.4049/jimmunol.180.9.6402

Table

Table 1: Clinical and laboratory findings in patients with Zika virus–associated Multiple Sclerosis-like manifestations

	Patient 1	Patient 2	Patient 3	Patient 4
Clinical presentation				
Age	30	51	48	57
Sex	Male	Male	Male	Female
Medical history	None	None	None	None
Viral prodrome	Fever and myalgia	Acute fever and rash	Acute fever and rash	Fever, intense myalgia and skin rash
Neurologic MANIFESTATIONS	Paresthesia and headache	Paraparesis, that evolved into tetra paresis.	Tetra paresis And ataxia.	Visual loss and walking impairment
Time from viral prodrome to neurologic symptoms	5 days	11 days	10 days	11 days
Neurologic examination				
	Hypoesthesia right upper limb and bilateral optic neuritis	Dysarthria, tetra paresis and drowsiness	Tetra paresis, Ataxia and disorientation	Spastic symmetric crural paraplegia, optic neuritis with left visual loss
Diagnostic studies				
Zikv RT-PCR	Negative	Negative	Negative	Positive
IgM ZikV	Negative	Positive in the serum	Positive in the serum	Positive in the serum
IgG ZikV	Positive in the serum	Positive in the serum	Positive in the serum	Negative in the serum
CSF	8 leukocyte/mm^3 , 27 mg/dl protein, OCB positive, IgG index 0,88	0 leukocytes/mm^3, 27 mg/dl protein.	15 leukocytes/mm^3, 71 mg/dL protein, and 55 mg/dL glucose	9 leukocyte/mm^3 , 64 mg/dl protein, OCB negative, AQP4 Ab Negative

Figures

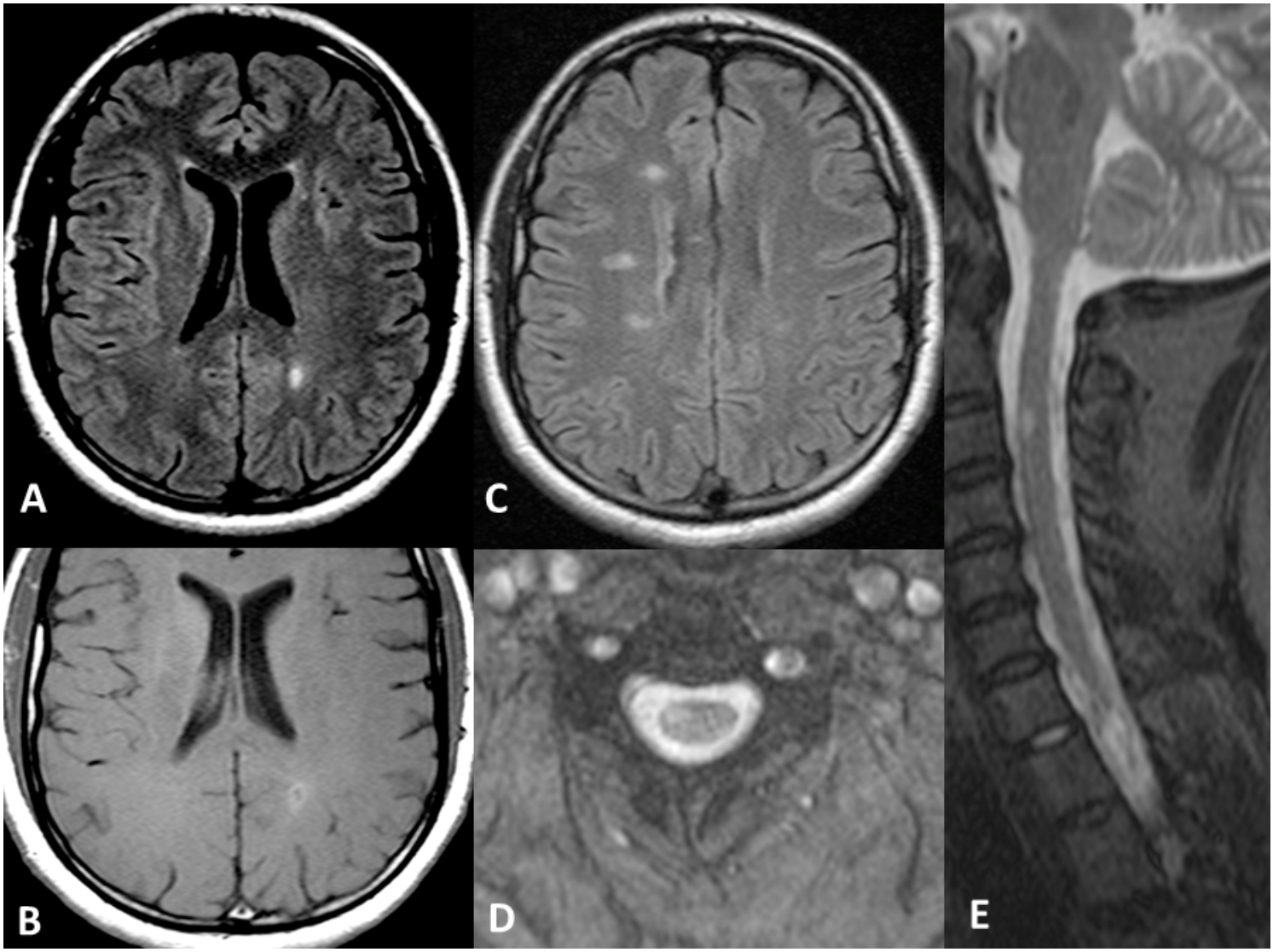

Figure 1

Patient 1 MS like pattern. A focal subcortical hyperintense FLAIR lesion (A) with contrast enhancement (B) is observed in conjunction with other periventricular and pericalosal bright lesions (C), similar to Dawson's fingers described for MS disease. Cervical lesions follow the same pattern, eccentrically located in the T2* axial plane (D) and extending for one vertebral body dimension on the sagittal STIR cervical image (E).

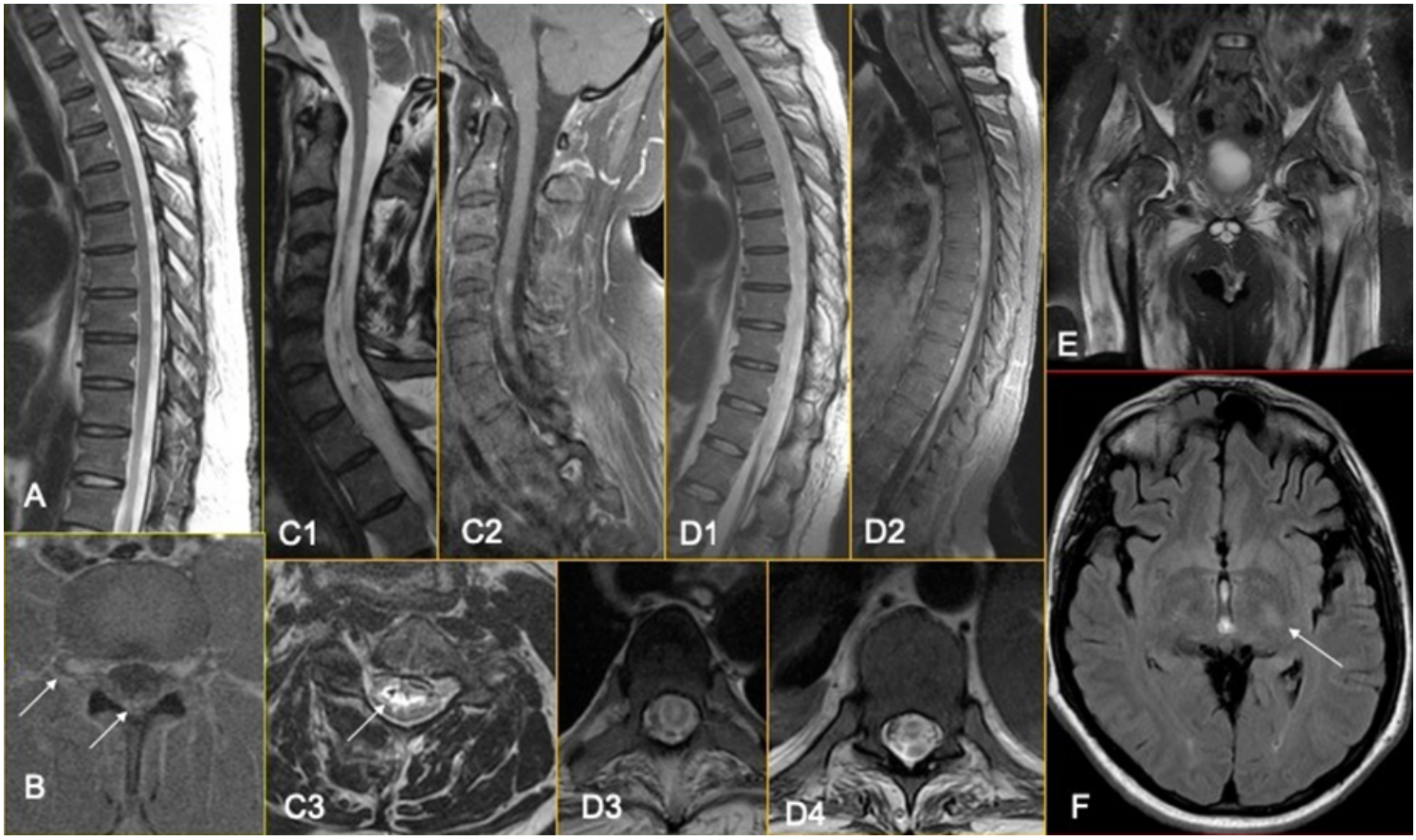

Figure 2

Patient 2 Lower limbs flaccid paralysis followed by extensive myelitis. Initial dorsal MRI (A) was normal, and a significant contrast enhancement was observed in the axial T1 fat-sat image of the lumbar spine, involving the dorsal ganglia and the lumbo-sacral plexus inside the spine canal (B). After 3 months of evolution the patient developed longitudinal extensive transverse myelitis (C, D), already with focal tapering of the cervical/dorsal transition on sagittal STIR (C1), remembering a sequel area. The lesion was centrally located (C3, D3), with anterior horn involvement (D4) and signals of previously bleeding inside the central canal (C3). A patch and irregular contrast enhancement was noticed along the sequel area (C2) and along the entire dorsal spinal cord (D2). Consequent muscle denervation was observed in the coronal STIR of the pelvic girdle muscles (E) and ascendant cortical-spinal tract degeneration consequent to the spinal cord damage on FLAIR axial images (F).

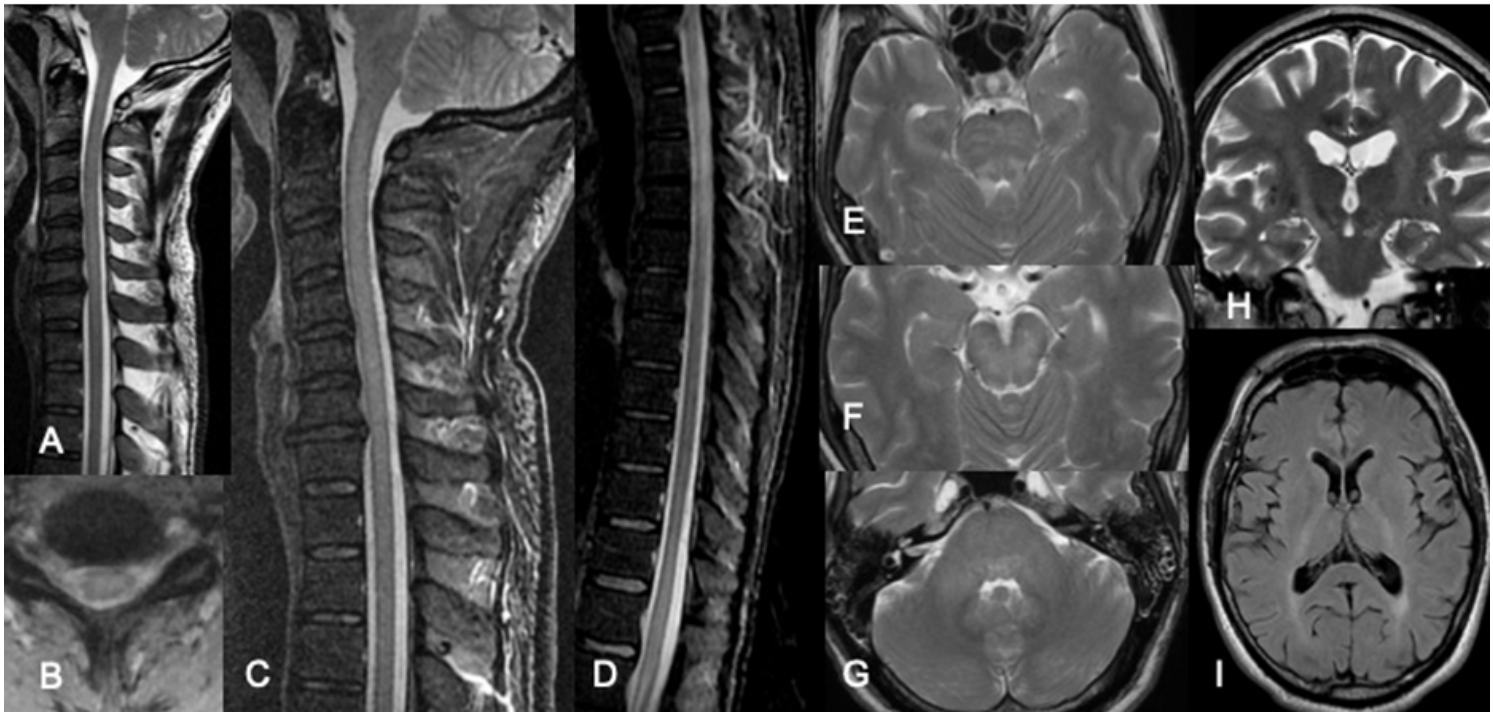

Figure 3

Patient 3 Longitudinal extensive transverse myelitis. Cervical spinal cord sagittal T2 (A) show extensive continuous high signal intensity lesion affecting the hole diameter of the spinal cord on axial T2* images (B), best identified on sagittal STIR (C). The extent of more than 3 vertebral body was confirmed, as well as the involvement of the medullary cone on sagittal STIR (D). Brain lesions were mainly detected affecting the brain stem on axial T2 images, including the posterior aspect of the mesencephalon (E), pons (F) and the medial cerebellar peduncle (G). Two years follow up brain images show hypersignal intensity on coronal T2 (H) and axial FLAIR (I) images located in the cortical-spinal tract, mostly associated with retrograde degeneration within the spinal cord lesions.

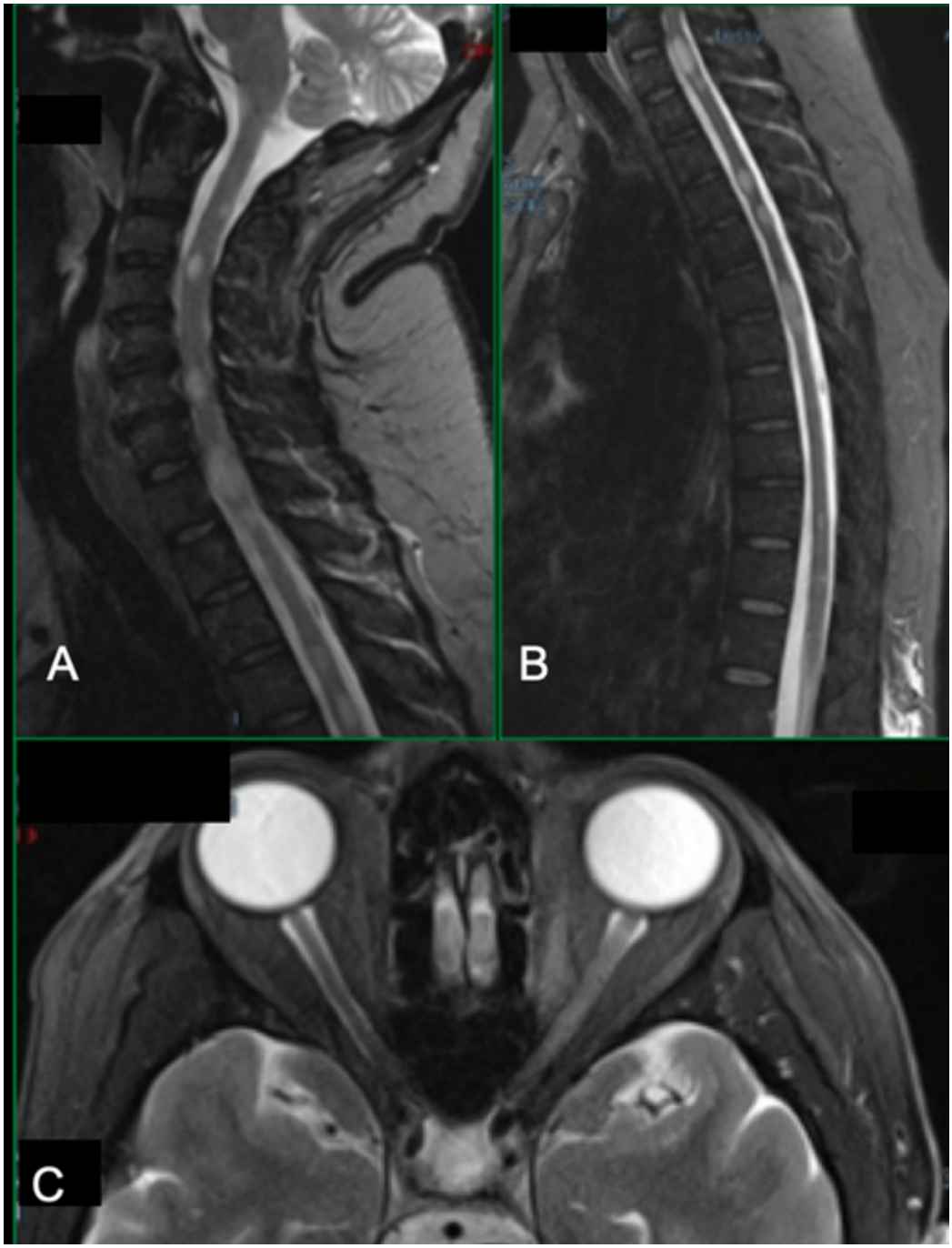

Figure 4

Patient 4 Tumefactive myelitis. Sagittal STIR cervical (A) and dorsal (B) spinal cords have multiple small tumefactive bright lesions, randomily affecting all main cords tracts, diffusively distributed. Axial T2-fat suppressed at the orbital area shows bright thickening of the intra-orbital extent of the left optic nerve, reflecting extensive optic neuritis.

A

```
NS5   261 HQDELIGRARVSPGAGWSIRETACLAKSYAQMWQLLYFHRRDLRLMANAI    310
          |.|:.:|                  :..:...:|.|::           .
PLP   148 HPDKFVG----------------ITYALTVVWLLVF----------A    168

NS5   311 CSSVPV    316
          ||:|||
PLP   169 CSAVPV    174
```

B

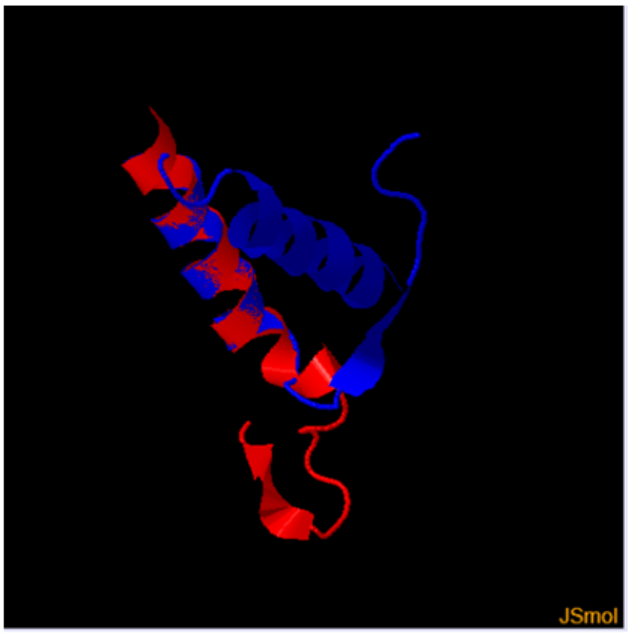

Figure 5

Results of alignment between NS5 antigen of ZikV (AJD79051.1) and PLP MS autoantigens. Alignment of amino acid using EMBOSS needle. Note the motif highlighted have 83% identity (A). Structural alignment between PLP131-198 and NS5281-325 proteins. In red the PLP131-198 is represented and in blue the NS5281-325 (B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx