

The Guillain–Barrè peptide signatures: from Zika virus to *Campylobacter*, and beyond

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Abstract: Scientific attention has focused recently on the link between Guillain–Barrè syndrome (GBS) and Zika virus (ZIKV). Two related questions emerged: 1) what triggered the violent 2014 outbreak of a virus, which, first identified in 1947, had caused only a limited number of documented cases of human infection until 2007 and 2) which molecular mechanism(s) relate ZIKV active infection to GBS, an autoimmune inflammatory polyradiculoneuropathy. Capitalizing on the increased interest on ZIKV and hypothesizing the involvement of autoimmune mechanisms, we searched for minimal epitopic determinants shared between ZIKV and other GBS-related pathogens – namely, Epstein–Barr virus, human cytomegalovirus, influenza virus, *Campylobacter jejuni*, and *Mycoplasma pneumoniae*, among others – and human proteins that, when altered, have been associated with myelin disorders and axonopathies. We report a considerable peptide matching that links GBS-related pathogens to human proteins related to myelin disorders and axonopathies. Crucially, the shared pentapeptides repeatedly occur throughout numerous epitopes validated as immunopositive by a conspicuous scientific literature. The data support a scenario where multiple different infections over time and resulting multiple cross-reactions may contribute to the pathogenesis of GBS. In practice, previous infection(s) might create immunologic memory able to trigger uncontrolled hyperimmunogenicity during a successive pathogen exposure. ZIKV pandemic appears to be an exemplar model for a proof-of-concept of such multiple cross-reactivity mechanism.

Keywords: peptide sharing, GBS-related human proteins, GBS-related pathogens, multiple cross-reactivity, hyperimmunogenicity

Introduction

Zika virus (ZIKV) was discovered in 1947 and has been considered of little or no clinical importance until 2007, a date that marks the beginning of epidemics that caught scientific and clinical communities by surprise.¹ Among the pathologic sequelae, Guillain–Barré syndrome (GBS) in adults appears to be a clinical outcome following ZIKV active infection.^{2–7}

How this neuropathologic outcome and the flavivirus infection may be linked at the molecular level is unknown. Actually, some authors have even interpreted the co-occurrence of ZIKV infection and GBS as a temporal coincidence rather than a causal relation.⁸ The issue is further complicated by the fact that GBS – although described for the first time in 1859⁹ – still presents, beyond its association with ZIKV, a largely unknown etiology. Genetic factors have been hypothesized to constitute a causal platform leading to the disease.^{10,11} However, research on candidate genes that could plausibly be involved in the pathogenesis of GBS has not been conclusive. For

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instance, increased susceptibility to GBS in association with polymorphisms in CD1, low-affinity immunoglobulin gamma Fc region receptors II-a and II-b (FcRII-a and FcRII-b),^{12–14} and interleukin-10 genes still awaits validation.^{15–17}

In parallel, a large body of research has investigated the possible association between GBS and infections. In particular, *Campylobacter jejuni* and *Mycoplasma pneumoniae* infections have been related to the disease,^{18–22} most possibly through autoimmune cross-reactive mechanisms.^{23–26} At a lesser extent, human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) might also be involved in GBS. Indeed, although many reports did not relate HCMV to GBS,^{27–29} nonetheless, numerous cases of HCMV-GBS association have been described in transplant recipients and during pregnancy.^{30–36} Moreover, a prospective cohort study described 63 (12.4%) HCMV-GBS cases out of 506 patients with cases of GBS, with patients with HCMV-GBS more likely to be young – <35 years old in most of the cases – and female.³⁷ Similarly, numerous clinical case reports describe GBS associated with EBV infection.^{38–42}

However, it remains unclear how such infectious pathogens – which are largely widespread and sluggishly latent worldwide^{43–48} – can, all of a sudden, attack the host causing the complex pathologic picture of the GBS.

Based on the autoimmune context that connects infections to GBS, we recently analyzed ZIKV polyprotein for peptide sharing with human proteins that, when altered, may associate with GBS-like syndromes and found large peptide overlap suggestive of a great potential for autoimmune cross-reactivity.⁴⁹ Here, we use the peptide platform common to ZIKV and GBS-associated human proteins and search for minimal immune determinants that are additionally shared with infections related to GBS such as the above-mentioned *C. jejuni*, HCMV, EBV, and *M. pneumoniae*. The scientific rationale is that different infectious pathogens might evoke a succession of immune responses converging on identical epitopic sequences and characterized by a progressively more rapid production of increasingly powerful antibodies on subsequent encounters with the same epitopic targets. Then, sharing of identical cross-reactive epitopes with host proteins can result in amplified cross-reactions and consequent severe diseases, thus explaining the violence of the otherwise asymptomatic ZIKV infection.⁵⁰

Methods

Analyses were conducted on human proteins related to GBS and retrieved from UniProtKB Database (<http://www.uniprot.org/>)⁵¹ using “myelin, (de)myelination, axonal neuropathy” as

keywords (Table S1), as already detailed elsewhere.⁵⁰ References for disease involvement are available at <http://www.uniprot.org/>. Human proteins are indicated by the UniProt Accession name.

A set of pathogen proteomes was chosen for analyses based on the following criteria:

- belonging to infectious agents that have been reported as related to or concomitant, even occasionally, with GBS, ie, *C. jejuni*,^{18,19} *M. pneumoniae*,^{18,20–22} HCMV,^{18,30–37} EBV,^{18,38–42} hepatitis E virus, genotype 1 (HEV),⁵² human papillomavirus type 16 (HPV16),⁵³ influenza viruses,⁵⁴ dengue virus (DENV),⁵⁵ West Nile virus (WNV),⁵⁶ yellow fever virus (YFV),⁵⁷ and varicella zoster virus (VZV);⁵⁸
- for which proteome completeness has been established;
- with experimental evidence at protein level;
- belonging to the Swiss-Prot section reviewed by UniProtKB.

The pathogen proteomes are as follows (in alphabetical order, with abbreviations, number of proteins, number of amino acids (aa), and taxonomy ID): *C. jejuni*, 1623 proteins, 507643 aa (192222); DENV, 10 proteins, 3392 aa (11059); EBV, 109 proteins, 51458 aa (10377); HEV, 3 proteins, 2467 aa (652674); HCMV, strain Merlin, 168 proteins, 63460 aa (295027); HPV16, 8 proteins, 2426 aa (333760); influenza A virus, H1N1, 12 proteins, 4788 aa (211044); influenza A virus, H5N5, 12 proteins, 4809 aa (93838); influenza B virus, 11 proteins, 4718 aa (518987); *M. pneumoniae*, 687 proteins, 239888 aa (272634); VZV, 69 proteins, 35782 aa (10338); WNV, 13 proteins, 3430 aa (11082); YFV 13 proteins, 3411 aa (11090); and ZIKV, 13 proteins, 3419 aa (64320). Proteomes are described in detail at <http://www.uniprot.org/>.⁵¹

Peptide matching analyses were conducted using the pentapeptide as a minimal immune unit^{59–61} and utilizing the elsewhere described pentapeptide platform shared between ZIKV and human proteins that, when altered, may associate with GBS.⁴⁹ In brief, GBS-related proteins were obtained from UniProtKB⁵¹ using the keywords “myelin, (de)myelination, axonal neuropathy”. Then, the primary aa sequence of each ZIKV protein was dissected into pentapeptides overlapping each other by four residues. For example, ZIKV protein C (Q32ZE1, aa 2–104, KNPKEEIRRIRIVNMLKRGVARVNPLGGLKRLPAGLLLGHPIRMVLAFLRFTAIPSLGLINRWGS-VGKKEAMEIHKFKKDLAAMLRIINARKERKRR) was sequentially dissected into KNPKE, NPKEE, PKEEI, KEEIR, and so forth until its last pentapeptide ERKRR, for a total of 99 pentamers. At the end, the 12 ZIKV proteins

(prM considered as one protein) yielded 3370 pentapeptides. The same procedure was applied to calculate the number of pentapeptides present in the pathogen proteomes described earlier.

The 3370 ZIKV pentapeptides were probed for occurrences within the set of human proteins related to GBS using PIR peptide match program (<http://research.bioinformatics.udel.edu/peptidematch/index.jsp>).⁶² A total of 222 ZIKV pentapeptides were found to occur throughout 97 human proteins related to GBS. The 97 human proteins related to GBS and sharing pentapeptide(s) with ZIKV have been previously detailed.⁴⁹

The pentapeptide platform common to ZIKV and GBS-related proteins was used to search for commonalities with GBS-related pathogens. That is, each of the 222 ZIKV pentapeptides shared with the 97 GBS-related proteins was analyzed for occurrences in the pathogen proteomes of infectious agents that had been selected as described earlier.

The immunological potential of the peptide sharing was investigated using the Immune Epitope Database (IEDB;

www.iedb.org) resource.⁶³ Only epitopes that had been experimentally validated as immunopositive in the human host were considered.

Results

Pentapeptide(s) common to ZIKV, GBS-related human proteins, and GBS-related pathogens.

Table 1 shows the occurrences of the ZIKV pentapeptides shared with the 97 GBS-related proteins in the analyzed infectious agents. It can be seen that, with the exception of influenza B virus, the analyzed GBS-associated pathogens share pentapeptides common to ZIKV and human GBS-related proteins.

Numerically, 135 out of 222 pentapeptides shared between ZIKV and the set of human GBS-related proteins occur and often recur throughout the pathogens under analysis for a total of 206 multiple occurrences. As previously observed,^{64–67} such pentapeptide sharing is extremely high

Table 1 Pentapeptides common to ZIKV, GBS-related human proteins, and GBS-related pathogens

Pentapeptides ^a	Pathogen
–	Influenza B virus
EEIRR , PTQGS	Influenza A virus (H5N1)
ASSLV , EEIRR	Influenza A virus (H1N1)
TLETI, TVEVQ	HPV16
AAARA , ALRGL , LAAAV , LRGLP , RLAAA	HEV, genotype 1 ^b
AEEVL, ALAGA , ALAGG , GERAR, LAGAL , LLSLK, LLVVL , SPGAG , TAVSA, VLTAV	EBV
EALIT, FATTI, GAALR, GAGKT , GALEA , IFLST, ILAAL , LLLGR , LLLLT , LRIIN, RRLG, TVSLG, VLTAV	VZV
AAARA , EEEKE, EEIRR , FDLEN, GAALG, GAGKT , GEAAA , GTVSL, ILAAL , LLALA, LLGLL , LLLGR , LQDGL , LTAVR, LTCLA, LWLLR, SLGLD, STSQK, TAVSA, TVSLG	HCMV
AAAIF , AARGY , CSAVP , DRRWC, EFEAL , EFGKA , ETLGE, GCGLF , GDTAW , GEAAA , GETLG, GPSLR , GRARV , GSASS , GVPLL, LNDMG, NSTHE , QRGSG , RDLRL , RGYIS , RRDLR , RRWCF , RVILA , SAVPV , TAAGI , YISTR	DENV
AAAIF , AALGA , AARGY , ALAGA , ALGAI , ALRGL , ALVAV , ASAGI , ASSLV , CSAVP , DENHP , DRRWC, EALRG , EFEAL , EFGKA , ESSSS , FATTI, GAGKT , GCGLF , GDTAW , GEAAA , GRARV , GSASS , KGIGK , LAAAV , LRGLP , LVNGV , NSTHE , PRRLA , QRGSG , RDLRL , RGYIS , RRDLR , RRWCF , SAVPV , SLFGG , SPGAG , TAAGI , TEVEV , TKEEF , VEGLG , VSRGS , VTLGA , YISTR	WNV
EFEAL , EFGKA , ESSSS , GAGKT , GCGLF , GDTAW , LKDGR , NSTHE , QRGSG , TKEEF	YFV
AAAIF , AAARA , ALAGG , ALEAE, ALGAI , ALGLT, DGLSE, EEARR, EGLKK, ENEAL, ESSSS , EVEET, GAGKT , GALEA , GLKRR, GPSLR , GSASS , IILLV, ILAAL , ILLMV, ISALE, KEVKK, LAAAV , LALAG , LKDGR , LKGKG, LLAVP, LLGLL , LLLLT , LLTTA, LLVVL , LQDGL , LVEED, LVILL, NGVQL, PTQGS, RLAAA, RRALK, SLGLD, TEVEV , TKEEF , VEFKD, VVDPI, VVGLL	<i>M. pneumoniae</i>
AALGA , AKVEV, ALAGA , ALAGG , ALGAI , ALGLT, ALKDG, ALVAV , ASAGI , ASSLV , DENHP , DGLSE, EALIT, EALRG , EEEKE, EELEI, EFEAL , EGLKK, EKEWK, ENEAL, ENIKD, FDLEN, GAALG, GAGKT , GALEA , GEAGA, GETLG, GGGTG, GIMLL, GPSLR , GSASS , GTLPG, IFLST, IILLV, ILAAL , ILLMV, KEVKK, KGIGK , KGSVL, KKSGL, KNPKE, LALAG , LALGG, LALGG, LDFSD, LKGKG, LLALA, LLAVP, LLGLL , LLLGR , LLLLT , LLSLK, LLVVL , LRIIN, LSTQV, LTAVG, LVILL, LVNGV , MLLSL, PRRLA , PSLGL, RRALK, RVILA, SEELE, SLFGG , SLGLI, STSQK, STTAS, TAAGI , TEVEV , TKEEF , TLETI, VEEDG, VEFKD, VEGLG , VLSMV, VNPLG, VRAAK, VSRGS , VTLGA , VVGLL, YLSTQ	<i>C. jejuni</i>

Notes: ^aPentapeptides with multiple occurrences in bold. ^bTwo HEVs, genotype 3, taxonomy IDs 509615 and 512345, share only 2 pentapeptides (ALRGL and LRGLP).

Abbreviations: ZIKV, Zika virus; GBS, Guillain-Barré syndrome; HPV16, human papillomavirus type 16; HEV, hepatitis E virus, genotype 1; EBV, Epstein-Barr virus; VZV, varicella zoster virus; HCMV, human cytomegalovirus; DENV, dengue virus; WNV, West Nile virus; YFV, yellow fever virus.

and unexpected given that the probability E of a ZIKV pentapeptide to occur simultaneously in the set of the 13 GBS-related pathogens and in the set of the 97 human GBS-related proteins is $6977141836772461e-6$, ie, it is close to zero (Box 1). This infinitesimally low value is in sharp contrast with the actual data displayed in Table 2. As a matter of fact, Table 2 highlights an intense pentapeptide sharing that underlies a multiple cross-reactivity platform among the analyzed pathogens and the human host.

Immune potential of the pentapeptides common to ZIKV, GBS-related human proteins, and GBS-related pathogens

Such a high potential for cross-reactions appears likely also in view of the fact that most of the 135 pentapeptides detailed in Table 2 not only often recur among the GBS-related pathogens (eg, the pentapeptides EEIRR, AAARA, ALAGG, GAGKT, GALEA, GPLSR, and GSASS given in bold in Table 1) but are also present in hundreds of epitopes experimentally validated as immunopositive in the human host. Table 2 shows a limited representative list of such immunopositive epitopic sequences.

Discussion

Starting from 2000,⁶⁴ our laboratory described a massive peptide overlap between proteins from infectious agents and the human proteome,⁶⁵ thus calling attention to the cross-reactivity issue in immunology. In fact, the magnitude of such a peptide

sharing leads to predict a high extent of cross-reactive immune responses following infections in the human host.^{66–72}

Here, we focus on the issue of multiple cross-reactivity and analyze the molecular connections between infectious pathogens related to GBS. We report on the presence of minimal immune determinants in the human host and repeatedly shared among infectious agents so different as the flaviviruses ZIKV, DENV, WNV, and YFV and the bacteria *M. pneumoniae* and *C. jejuni*. Such intrapathogen peptide commonality may originate multiple cross-reactions having the same peptide sequences as epitopic targets. The immunological implications are that immune responses elicited by different successive infections may add up with intensified avidity and affinity at the level of cross-reactive sites, thus exacerbating autoimmune attacks in the host.

The extent of the autoimmune damage emerges from the analysis of the human proteins involved in the sharing, most of which are crucial components of the neurological network. An example among the many is the pentapeptide LAGAL that is shared by ZIKV, EBV, *M. pneumoniae*, and *C. jejuni* and is also present in three human proteins involved in myelin disorders, ie, CGT, GFAP, and MTMR2 (Tables S1 and S2).

- CGT or 2-hydroxyacylsphingosine 1-beta-galactosyltransferase is involved in the synthesis of sulfatide 3-O-sulfogalactosylceramide,⁷³ which is essential for paranodal junction formation and for the maintenance of ion channels on myelinated axons.⁷⁴ Of note, the sulfatide blocks the binding of *C. jejuni* DNA-binding protein to

Box 1 Theoretical probability E of a ZIKV pentapeptide to occur simultaneously in the set of the 13 GBS-related pathogens and in the set of the 97 human GBS-related proteins under analysis

The expected number of times E that one pentapeptide occurs in a protein is directly proportional to the number p of pentapeptides in the protein and inversely related to the number N of all possible pentapeptides, with N equal to 20^5 since each pentapeptide residue can be any of 20 aa and assuming that all aa occur with the same frequency: accordingly, such expected number of times E is given by equation

$$E = \frac{p}{N}$$

By considering two proteins, 1 and 2, of pentapeptide size p_1 and p_2 , and two events E1 and E2 – that are assumed to be independent – that a same pentapeptide will be selected simultaneously in both proteins 1 and 2, then the expected number of times E is given by

$$E = E1 \cdot E2 = \frac{p_1}{N} \cdot \frac{p_2}{N} = \frac{p_1 \cdot p_2}{N^2}$$

In the case in point, the expected number of times E that a ZIKV pentapeptide will be simultaneously present in the set formed by the 97 human GBS-related proteins (Table S1) and in the set of the 13 GBS-related pathogen proteins is given by the formula:

$$E = \frac{p_{\text{ZIKV}} \cdot p_{\text{human}} \cdot p_{\text{pathogens}}}{N^3}$$

where $p_{\text{ZIKV}} = 3370$ (no of ZIKV pentapeptides), $p_{\text{human}} = 74004$ (no of pentapeptides contained in the set of 97 human GBS-related proteins), $p_{\text{pathogens}} = 916732$ (no of pentapeptides contained in the set of proteins from the 13 GBS-related pathogens), and $N^3 = 20^{15}$ (with N equal to 20^5). Solving the equation, one obtains $E = 6,977141836772461e-6$.

Abbreviations: ZIKV, Zika virus; GBS, Guillain-Barré syndrome; aa, amino acids.

Table 2 Epitopes experimentally validated as immunopositive in the human host and containing pentapeptide(s) common to ZIKV, GBS-related human proteins, and GBS-related pathogens

IEDB ID ^a	Epitope ^{b,c}	IEDB ID ^a	Epitope ^{b,c}
10	aaAAAIvfi	446920	nIISALEea
2859	alRGLPiry	452231	ALAGGitmv
3546	apfdETLGEedkdld	452923	aseALAGAL
9980	dRGIYSqy	454329	gSLGLlfa
11125	EALRGLPir	454747	illdhEKEWKI
14278	ESSSSdtkp	455521	kLQDGLlhi
15968	fGDSYI	456221	LLAVPvpgv
19121	GDSYli	456552	lprgLAGAL
21271	gmGAAAAIF	458233	rlvGIMLLI
21783	GPSLRttttv	459912	tlDENHPSi
24302	hlsLRGLPv	460498	vpAAARAgai
36077	IGDTAW	462972	ALAGApypqa
37757	llrSTSQK	464145	dyPALLVv
42819	mTKEEFtry	465337	ftASAGlqv
43963	nGCGLF	465643	GLDFSlpgm
47494	PFGDSy	467239	kLEGDLtgpsv
59141	slglVILLvl	469571	qpEGLKKtl
59561	sLVNGVvrl	470656	sLLTTAevvv
62564	syhDRRWCF	471899	tpfGGGTGgf
64181	tiaydEEARR	472107	TVSLGgfeitppv
71730	vlaGAALGvataaq	475411	AETDEprll
76146	ytpgsclagvIEALIThrqe	475437	aeVEGLGkqva
95619	ngtrrtVNPLGf	475912	apSSTSQel
108957	fLLGLLffv	477278	EEEEErntaa
113368	elilydkEEIRri	478632	gidSSSEv
118521	mILKKGkdkaqie	479191	hENEALwreva
133702	srNSTHEmy	480858	klrEEARRk
162369	gQRGSgssf	481247	KTKDGvrev
162647	kEVEETata	483586	qSTTASlkk
162892	lpktGTVSL	483862	rEFGKAlql
176418	rALEAEkralw	484166	RLAAAarek
179238	maflrsvsRLAAAVf	485074	ryiEGLKKR
179920	vvRDLRLra	485864	sfSPGAGaf
180696	pasiAARGYi	486103	SLFGGrtsgl
180816	wgnCGCLFgkggivt	486146	sLLALAGAv
182553	allaLNDMGk	487020	sVSRGSslk
185931	tkqtGSASSm	487072	sygpGPSLR
188820	avgtgtGAALGAgigALAGG	487689	trhKEVKKI
188921	mntkiatrlsvfALAGAla	488045	VEEDGqllsl
194401	tLAAAVpki	488605	vVVDPIlsv
195482	iGETLGEkwksrlna	491301	GRARVsvv
207331	ELGKRvqal	492165	hrALVAVII
209443	gesGAGKTW	493078	lrfpNGVQL
213577	ktfTAAGI	494432	rrILLLLTI
217605	REEGAvdkysy	506799	LLTRScail
220715	vEVQLLeskty	506908	IPRRLAiqI
220742	vGAALRpaf	510341	ypASSLVv
222394	GEAGAiervl	515064	epGEEAAaggaaEEARR
222457	geGLLIVkv	536076	GTLPGsaepplTAVR
222756	heySEEEkl	539058	ahftdpssvAARGYIS
222989	kegyVLTAV	539081	ALRGLPvry
236364	VRAAKfwk	539140	CSAVPVdw
420040	qnpqLLAAL	539287	GEAAAIvmt
420274	tPTQGSvl	539600	lmyfhRRDLRLasna

(Continued)

Table 2 (Continued)

IEDB ID ^a	Epitope ^{b,c}	IEDB ID ^a	Epitope ^{b,c}
423402	IFATTLfigympihc	541359	dAALGAeem
423807	aaaVVGLLy	541798	eLLSLKy
424246	EEARRLLGy	542210	GAALRGLsl
427527	stTAVSAry	542311	ghtLLALAt
427966	twAVLLRy	542373	gLKDGvall
435741	sRVILAgnl	544887	RRLLGkykf
436632	aTLETllrh	546136	vLRIIINeptaai
437505	GEAAAkeew	548062	elkLRGLPvsgt

Notes: ^aEpitope IEDB IDs are listed in ascending numerical order. Details and references are available at <http://www.iedb.org/idsearch.php>. ^bEpitope peptide sequences are given in one letter code. ^cShared peptide fragments are given in capital letters.

Abbreviations: ZIKV, Zika virus; GBS, Guillain-Barré syndrome; IEDB, Immune Epitope Database.

myelinated nerves, a reaction that has been associated with *C. jejuni*-related GBS;⁷⁵

- GFAP or glial fibrillary acidic protein has been reported to be a marker of axonal GBS and outcome;⁷⁶
- Myotubularin-related protein 2 (MTMR2) is a phosphoinositide-3-phosphatase that, if altered, associates with demyelinating peripheral neuropathy characterized by excessive redundant myelin, also known as myelin outfoldings.^{77,78} MTMR2 appears to negatively regulate membrane homeostasis in Schwann cell myelination.⁷⁹

Another myotubularin-related protein, namely MTMR5, shares eight pentapeptides with ZIKV (eg, AVLLR, GPSLR, GLLIV, LQDGL, REEGA, SEELE, SLGLI, and VLSMV) and many of the said pentapeptides are also present in infectious agents (Table 1). MTMR5 pentapeptide sharing is noteworthy. Indeed, alterations of MTMR5 are involved in demyelinating neuropathies⁷⁹ and, in addition and most interestingly, lead to impaired spermatogenesis.^{80–82} This datum might be a hint for widening the study of the still obscure reasons for gender differences in GBS pathogenesis.⁸³ In this perspective, also future studies that extend analyses to non-peptidic GBS epitopes warrant attention. For example, B4GN1 or beta-1,4-*N*-acetylgalactosaminyltransferase 1 plays a role in spermatogenesis and, when altered, in male infertility;⁸⁴ is involved in the biosynthesis of gangliosides⁸⁵ and produces a ceramide trisaccharide (*N*-acetyl-d-galactosaminyl-(*N*-acetylneuraminy)-d-galactosyl-d-glucosylceramide) that is present in non-peptidic structural GBS epitopes (IEDB IDs: 139429 and 143251).

Although space precludes a detailed discussion of the data reported in Table 1, a final note is due with regard to WNV that hosts 44 out of the 135 pentapeptides common to ZIKV and GBS-related human proteins (Table 1). WNV infections

may cause acute flaccid paralysis through a pathogenic mechanism that most possibly involves disrupted glutamate transporter expression in the spinal cord.⁵⁶ Hence, it draws our attention the presence of three pentapeptides (namely ALRGL, GAALR, and LLGLL) that are present in the amino acid transporter SATT (or SLC1A4 or ASCT1) (Table S2). SATT is essential in brain for d-serine transport⁸⁶ and is mostly expressed in hippocampal pyramidal and dentate granule neurons, and, in the cerebellum, Purkinje cells and their dendrites, thereby suggesting a role in pathophysiological processes that involve glutamate toxicity.⁸⁷ Indeed, activation of *N*-methyl-d-aspartate receptors (NMDARs) by synaptically released l-glutamate requires occupancy of coagonist binding sites in the tetrameric receptor by either glycine or d-serine, so that altered SATT and, thereby, altered d-serine flux in the brain would alter NMDAR activity. The hypothesis of a potential link between SATT-induced NMDAR alteration and flaccid paralysis seems to find a support in the fact that flaccid paraplegia has been observed in patients with autoantibodies to NMDARs.^{88–90}

Conclusion

We observe that the main caveats of the present research are the limited number of the analyzed pathogens and, in addition, the fact that, in front of the tendency of infectious pathogens to mutate, only representative taxonomy types have been analyzed. Hence, the level of intrapathogen multiple cross-reactivity might be even underestimated. A second limitation of the present study is given by the fact that it mainly analyzes peptidic epitopic sequence potentially related to GBS. As a matter of fact, the acute paralytic GBS is also characterized by autoantibodies against glycolipids and gangliosides.^{91,92}

Given these notes of caution, the present study offers a scientific rationale and a methodology to analyze the molecular role of intrapathogen sharing in the pathologic sequelae that may be associated with multiple infections. Indeed, the high serological cross-reactivity that exists among flaviviruses (eg, ZIKV, DENV, WNV, and YFV)^{93,94} exemplifies the possibility that different infections occurring at different times may sum up onto a same set of epitopic determinants and result in hyperimmunogenicity,^{95,96} possibly resulting in neurological damage.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 List of the 97 human proteins related to myelin, (de)myelination, and/or axonal neuropathies and sharing pentapeptides with ZIKV polyprotein (human proteins are reported by UniProt entry, a brief description of function, and aa length)

ABCD1. ATP-binding cassette sub-family D member 1. Adrenoleukodystrophy. Progressive multifocal demyelination of the CNS.	745
ACATN. Acetyl-coenzyme A transporter 1. Cerebral and cerebellar atrophy and hypomyelination.	549
ACY2. Aspartoacylase. White matter vacuolization and demyelination.	313
ADCY6. Adenylate cyclase type 6. Hypomyelination neuropathy.	1168
ANAG. Alpha-N-acetylglucosaminidase. Axonal neuropathies.	743
ARSA. Arylsulfatase A. Hydrolyzes cerebroside sulfate. Intralysosomal storage of cerebroside-3-sulfate, with a diffuse loss of myelin in the CNS.	507
CC177. Myelin proteolipid protein-like protein.	707
CGT. 2-Hydroxyacylsphingosine 1-beta-galactosyltransferase. Synthesis of galactocerebrosides, which are abundant in the myelin of the CNS and peripheral nervous system.	541
CH60. 60 kDa heat shock protein, mitochondrial precursor. Hypomyelinating leukodystrophy characterized by infantile-onset rotary nystagmus, progressive spastic paraplegia, neurologic regression, motor impairment, profound mental retardation.	573
CLCN2. Chloride channel protein 2 (CIC-2). Leukoencephalopathy with ataxia. White matter abnormalities on brain MRI suggesting myelin microvacuolation.	898
CLD11. Claudin-11. Oligodendrocyte-specific protein. Oligodendrocyte-specific protein is concentrated in CNS myelin, seems to modulate proliferation and migration of oligodendrocytes, is an autoantigen in the development of autoimmune demyelinating disease.	207
CMCI. Calcium-binding mitochondrial carrier protein Aralar1. Mitochondrial aspartate glutamate carrier 1. Epileptic encephalopathy, early infantile, characterized by global cerebral hypomyelination.	678
CN37. 2',3'-Cyclic-nucleotide 3'-phosphodiesterase. CN37 is the third most abundant protein in CNS myelin.	421
CNTN1. Contactin-1 precursor. Neural cell surface protein F3. Involved in the formation of paranodal axo-glial junctions in myelinated peripheral nerves. Myopathy, hypotonia, muscle weakness.	1018
CNTPI. Contactin-associated protein 1. Involved in the saltatory conduction of nerve impulses in myelinated nerve fibers; demarcates the paranodal region of the axo-glial junction; may have a role in the signaling between axons and myelinating glial cells. Axoglia disease characterized by degeneration of anterior horn neurons, extreme skeletal muscle atrophy, and joint contractures leading to various degrees of flexion or extension limitations.	1384
CNTP2. Contactin-associated protein-like 2. Function and pathology as for CNTPI.	1331
CTDPI. RNA polymerase II subunit A C-terminal domain phosphatase. Hypomyelination of the peripheral nervous system.	961
CTL1. Choline transporter-like protein 1. May be involved in myelin production.	657
CXB1. Gap junction beta-1 protein. Connexin-32. Associated with both demyelinating and axonal neuropathies.	283
CXG2. Gap junction gamma-2 protein. Connexin-46.6. Hypomyelinating leukodystrophy with symptoms of Pelizaeus–Merzbacher disease.	439
CXG3. Gap junction gamma-3 protein. Connexin-30.2. Expressed within myelinating glial cells of the CNS and peripheral nervous system.	279
DNJB2. DNAJ homolog subfamily B member 2. Axonal neuropathies. Muscle weakness and atrophy resulting in gait impairment and loss of reflexes due to impaired function of motor nerves.	324
DPYL2. Dihydropyrimidinase-related protein 2. Collapsin response mediator protein 2. Neurodegeneration.	572
DRP2. Dystrophin-related protein 2. Required for normal myelination and the formation of Cajal bands in myelinating Schwann cells.	957
DYHC1. Cytoplasmic dynein 1 heavy chain 1. Axonal neuropathy. Neuromuscular disorder characterized by degeneration of the anterior horn cells of the spinal cord, leading to symmetrical muscle weakness and atrophy.	4646
EGR2. E3 SUMO-protein ligase EGR2. Hypomyelinating/amyelinating neuropathies.	476
ENOG. Gamma-enolase. Has neurotrophic and neuroprotective properties on a broad spectrum of CNS neurons.	434
ENPP6. Ectonucleotide pyrophosphatase/phosphodiesterase family member 6. Choline-specific glycerophospho-diester phosphodiesterase.	440
EXOS8. Exosome complex component RRP43, cerebellar and corpus callosum hypoplasia, abnormal myelination of the CNS, and spinal motor neuron disease.	276
EZR1. Ezrin. Cytovillin. Expressed in cerebral cortex, basal ganglia, hippocampus, hypophysis, and optic nerve.	586
F168B. Myelin-associated neurite-outgrowth inhibitor. Modulates neurogenesis. Expressed in the brain, within neuronal axonal fibers, and associated with myelin sheets.	195
FA2H. Fatty acid 2-hydroxylase. Leukodystrophy.	372
FGD4. FYVE, RhoGEF, and PH domain-containing protein 4. Peripheral demyelinating neuropathies.	766
FIG4. Polyphosphoinositide phosphatase. Peripheral demyelinating neuropathies.	907
GDAP1. Ganglioside-induced differentiation-associated protein 1. Axonal neuropathies.	358
GDIA. Rab GDP dissociation inhibitor alpha. Oligophrenin-2.	447
GELS. Gelsolin. Gelsolin is specifically enriched in myelin-forming cells.	782

(Continued)

Table S1 (Continued)

GFAP. Glial fibrillary acidic protein. Leukodystrophy with macrocephaly, seizures, and psychomotor retardation	432
GNAO. Guanine nucleotide-binding protein G(o) subunit alpha. Epileptic encephalopathy. Brain abnormalities, such as cerebral atrophy or thin corpus callosum.	354
GPM6A. Neuronal membrane glycoprotein M6-a. Involved in neuronal differentiation, including differentiation and migration of neuronal stem cells.	278
GPR6. G-protein coupled receptor 6 (sphingosine-1-phosphate receptor GPR6). Blocks myelin inhibition in neurons.	362
HS71A. Associates with myelin basic protein and proteolipid protein in multiple sclerosis brains.	641
HS90A. Protection of oligodendrocyte precursor cells.	732
HSPB1. Heat shock protein beta-1. Axonal neuropathy.	205
HSPB8. Heat shock protein beta-8. Axonal neuropathy.	196
HTRA1. Serine protease HTRA1. Demyelination of the cerebral white matter with sparing of U fibers	480
HYCC1. Hyccin. Downregulated by CTNNA1 protein A. Leukodystrophy, hypomyelinating.	521
IL7RA. Interleukin-7 receptor subunit alpha. Multiple sclerosis	459
KIF1B. Kinesin-like protein KIF1B (Klp). Axonal neuropathy.	1816
LMNA. Prelamin-A/C.b Axonal neuropathy.	664
LMNB1. Lamin-B1 precursor. Axonal neuropathy.	586
LRSML1. E3 ubiquitin-protein ligase LRSML1.	723
Axonal neuropathies in the absence of myelin alterations.	
MAG. Myelin-associated glycoprotein precursor.	626
MAL. Myelin and lymphocyte protein.	153
MERL. Merlin.Moesin-ezrin-radixin-like protein. Neurofibromin-2. Schwannomin.	595
METK1. S-Adenosylmethionine synthase isoform type-1. Brain demyelination due to methionine adenosyltransferase deficiency.	395
MFN2. Mitofusin-2. Axonal neuropathy.	757
MPZL3 Myelin protein zero-like protein 3 precursor.	235
MRF Myelin regulatory factor.	1151
MRFL Myelin regulatory factor-like protein.	910
MTMR2. Myotubularin-related protein 2. MTMR2. Demyelination.	643
MTMR5. Myotubularin-related protein 5. Demyelination.	1867
MTMRD. Myotubularin-related protein 13. Demyelinating neuropathy.	1849
MYEF2. Myelin expression factor 2.	600
MYO1D. Unconventional myosin-1d. Expressed in myelinating oligodendrocytes.	1006
MYPR. Myelin proteolipid protein. It is the major myelin protein from the CNS. Hypomyelinating leukodystrophy.	277
MYT1. Myelin transcription factor 1. May play a role in: development of neurons and oligodendroglia in the CNS; differentiation of oligodendrocytes; regulation of myelin gene transcription.	1121
MYT1L. Myelin transcription factor 1-like protein. May play a role in development of neurons and oligodendroglia in the CNS.	1186
NDRG1. Protein NDRG1. Demyelinating neuropathy.	394
NFH. Neurofilament heavy polypeptide. Amyotrophic lateral sclerosis. Axonal degeneration in the absence of myelin alterations.	1026
NFL. Neurofilament light polypeptide. Demyelinating neuropathy.	543
NRCAM. Neuronal cell adhesion molecule precursor. Plays a role in the formation and maintenance of the nodes of Ranvier on myelinated axons.	1304
OPAL1. Opalin. Oligodendrocytic myelin paranodal and inner loop protein.	141
P5CR2. Pyrroline-5-carboxylate reductase 2. Hypomyelinating leukodystrophy.	320
PARD3. Partitioning defective 3 homolog, modulates peripheral myelination	1356
PRAX. Periaxin. Demyelinating neuropathy.	1461
PTPRC. Receptor-type tyrosine-protein phosphatase C. Multiple sclerosis.	1304
RPAC1. DNA-directed RNA polymerases I and III subunit RPAC1. Hypomyelinating leukodystrophy.	346
RPC1. DNA-directed RNA polymerase III subunit RPC1. Hypomyelinating leukodystrophy.	1390
RPC2. DNA-directed RNA polymerase III subunit RPC2. Hypomyelinating leukodystrophy.	1133
RTN4R. Reticulon-4 receptor. Receptor for myelin-associated glycoprotein. May play a role in regulating axonal regeneration and plasticity in the adult CNS.	473
S3TC2. SH3 domain and tetratricopeptide repeat-containing protein 2. Demyelinating neuropathy.	1288
SAP. Prosaposin. Demyelination, periventricular white matter abnormalities, peripheral neuropathy.	524
SATT. Neutral amino acid transporter A. Developmental delay, microcephaly and hypomyelination.	532
SCRIB. Protein scribble homolog. Regulates myelination and remyelination in the CNS.	1630
SDHA. Succinate dehydrogenase (ubiquinone) flavoprotein subunit, mitochondrial. Progressive leukoencephalopathy.	664
SMBP2. DNA-binding protein SMUBP-2. Axonal neuropathy.	993
STXB1. Syntaxin-binding protein 1. Brain hypomyelination.	594
SYAC. Alanine-tRNA ligase, cytoplasmic. Axonal neuropathy.	968

(Continued)

Table S1 (Continued)

SYDC. Aspartate-tRNA ligase, cytoplasmic. Hypomyelination and white matter lesions in the cerebrum, brainstem, cerebellum, and spinal cord.	501
SYG. Glycine-tRNA ligase. Axonal neuropathy.	739
SYHC. Histidine-tRNA ligase, cytoplasmic. Axonal neuropathy.	509
SYRC. Arginine-tRNA ligase, cytoplasmic. Leukodystrophy. Ataxia associated with diffuse hypomyelination apparent on brain MRI.	660
TEN4. Teneurin-4. Regulates the myelination of small-diameter axons in the CNS. Essential tremor.	2769
TNR1A. Tumor necrosis factor receptor superfamily member 1. Involved in multiple sclerosis.	455
TRIM2. Tripartite motif-containing protein 2. Axonal neuropathy.	744
TRPV4. Transient receptor potential cation channel subfamily V member 4. Axonal neuropathy.	871

Notes: Human proteins were retrieved using "myelin, (de)myelination, axonal neuropathy" as keywords. Proteins are indicated by UniProtKB/Swiss-Prot entry names, aa length, and listed in alphabetical order. Details and references for disease involvement are available at <http://www.uniprot.org/>.

Abbreviations: ZIKV, Zika virus; aa, amino acids; CNS, central nervous system; MRI, magnetic resonance imaging.

Table S2 Pentapeptide platform shared by ZIKV polyprotein and human proteins related to myelin, (de)myelination, and/or axonal neuropathies: 222 ZIKV pentapeptides (in bold) recur throughout 97 proteins (in parentheses as UniProt entry names)

AAAAR (CXG3); **AAAIF** (GELS); **AAARA** (NFH); **AALGA** (GPR6); **AARGY** (ARSA); **AEEVL** (SYG); **AEMEE** (MTMR2); **AETDE** (TEN4); **AGGFA** (PRAX); **AKFTC** (CXG2); **AKVEV** (NFH); **ALAGA** (ARSA; CLCN2; GPM6A); **ALAGG** (DPYL2); **ALEAE** (CTDPI; SCRIB); **ALGAI** (NRCAM); **ALGLT** (ANAG); **ALKDG** (TEN4); **ALRGL** (SATT); **ALYAV** (SYDC); **APAYS** (F168B; HSPB1); **ARRAL** (LMNB1; MYEF2); **ASAGI** (MRF); **ASDSR** (ANAG); **ASSLV** (MAL); **AVLLR** (MTMR5); **CRECT** (TRIM2); **CSAVP** (MYPR); **CYSQL** (IL7RA); **DENHP** (MTMR5); **DGLSE** (FIG4); **DHSGK** (DRP2); **DIEMA** (SYDC); **DRRWK** (TRPV4); **DTVNM** (CXG3); **EALIT** (CTL1); **EALRG** (SCRIB); **EDVNL** (RPC2); **EEARR** (ABCD1; EZRI); **EEKE** (DYHCl; HS90A; NFH); **EEIRR** (MFN2); **EELI** (MRFL); **EEPML** (CXG2); **EFEAL** (EZRI); **EFGKA** (MYO1D); **EGLKK** (TRIM2); **EKEWK** (SYRC); **ELGKR** (FGD4); **ENEAL** (MRFL); **ENIKD** (DYHCl); **EPARI** (SCRIB); **ERLQR** (SMBP2); **ESSSS** (MTMRD); **ETLGE** (SCRIB); **ETLHG** (NDRG1); **EVEET** (NFL); **EVQLL** (PRAX); **FATTL** (DRP2); **FDLEN** (ACY2); **FPDSN** (TRPV4); **FVVDG** (MYO1D); **GAALG** (CXG3); **GAALR** (CNTPI; SATT); **GAGKT** (DYHCl; MYO1D); **GALEA** (ANAG); **GCGLF** (SMBP2); **GDSYI** (GELS); **GDTAW** (SYAC); **GEAAA** (NFH); **GEAGA** (PRAX); **GERAR** (SMBP2); **GESSS** (GDIA); **GETLG** (SCRIB); **GGGCA** (CH60); **GGGTG** (RTN4R); **GIMLL** (CTL1); **GKRKR** (LMNB1); **GLDFS** (CMC1); **GLKKR** (MPZL3); **GLLIV** (MTMR5); **GPSLR** (MTMR5; HS90A); **GQVVT** (LMNA; PRAX); **GRARV** (GELS); **GSASS** (CC177; CXG2); **GSQHS** (IL7RA); **GTLPG** (RTN4R); **GTRGP** (SCRIB); **GTVSL** (PARD3); **GVPLL** (SMBP2); **HFSLG** (MFN2); **HSDLG** (MAG); **IAACL** (CLCN2); **IEPAR** (SCRIB); **IFLST** (DYHCl); **IILLV** (TRPV4); **IKDTV** (MERL); **ILAAL** (SAP); **ILAFL** (S3TC2); **ILLMV** (GPM6A); **IPGLQ** (S3TC2); **IPKSL** (KIF1B); **ISALE** (NRCAM); **ISRQD** (TEN4); **KEVKK** (EXOS8); **KGIGK** (RPAC1); **KGSLV** (SYAC); **KKSGI** (MYT1L); **KNPKE** (KIF1B); **KTKDG** (HSPB1; HSPB8); **LAHAV** (S3TC2); **LALAG** (CGT; GFAP; MTMR2); **LALGG** (P5CR2); **LDFSD** (CMC1); **LEERG** (FGD4); **LEGDL** (LMNB1); **LGLQR** (MYO1D); **LIYTV** (MTMRD); **LKDGR** (TEN4); **LKDGV** (SYHC); **LKGKG** (CH60); **LKMDK** (MERL); **LLALA** (ABCD1; ARSA; ENPP6; S3TC2); **LLAVP** (ACATN); **LLGLL** (CLCN2; CNTN1; SATT); **LLLGR** (HTRA1); **LLLLT** (CLD11); **LLSLK** (HYCCI); **LLTRS** (P5CR2); **LLTTA** (CH60); **LLVVL** (PTPRC); **LNDMG** (NRCAM); **LQDGL** (MTMR5); **LRGLP** (CN37); **LRIIN** (HS71A); **LSTQV** (ACATN); **LTAVG** (CXG2); **LTAYR** (RTN4R); **LTCLA** (IL7RA); **LYDRE** (KIF1B); **LVEED** (MYT1); **LVILL** (HS90A; TEN4); **LVNGV** (SYRC); **LWLLR** (ABCD1); **MAVLV** (ADCY6); **MLELD** (ENOG); **MLLSL** (ADCY6); **MSWFS** (ADCY6); **NAALG** (SDHA); **NGVQL** (SYRC); **NSFLV** (DPYL2); **NSTHE** (NRCAM); **PALLV** (CXBI; MTMR2; NDRG1); **PFAAG** (SCRIB); **PFGDS** (ARSA); **PRRLA** (P5CR2); **PSLGL** (PARD3; OPALI); **PTQGS** (CN37); **PVGRL** (CXG3); **PVILD** (SAP); **QLLYF** (TRPV4); **QRGSG** (CMC1); **RDLRL** (CLCN2; NFL); **REEGA** (MTMR5); **RFEEC** (MFN2); **RGECH** (TEN4); **RGYIS** (CH60); **RLAAA** (PRAX); **RPALL** (NRCAM; MTMRD); **RPASA** (RTN4R); **RRALK** (METK1); **RRDLR** (DYHCl); **RRLAA** (FA2H); **RRLLG** (MAG); **RRWCF** (TRPV4); **RVILA** (RPC2); **SAVPV** (MYPR); **SEELE** (MTMR5); **SGKRS** (MTMR2); **SLFGG** (CLCN2; GELS); **SLGLD** (ADCY6); **SLGLI** (FIG4; MTMR5); **SLRST** (DRP2); **SLTCL** (IL7RA); **SPGAG** (DNJB2); **SSSPE** (DYHCl); **SSTSQ** (HYCCI); **STSQK** (CNTP2); **STTAS** (EGR2); **TAAGI** (P5CR2); **TAVSA** (STXB1); **TEVEV** (MAG); **TKEEF** (CMC1); **TKNGS** (SMBP2); **TLETI** (TEN4); **TPVGR** (CXG3); **TQGSA** (ARSA); **TVDIE** (RPC2); **TVEVQ** (TNR1A); **TVSLG** (GPR6); **VATGG** (SDHA); **VDGDT** (CXG3; MYO1D); **VEEDG** (DNJB2); **VEFKD** (MYEF2); **VEGLG** (NRCAM); **VFIYN** (KIF1B); **VLDLH** (LRSM1); **VLSMV** (MTMR5); **VLTAV** (CXG2); **VNPLG** (PTPRC); **VPERA** (RTN4R); **VQLLA** (CMC1); **VRAAK** (NFL); **VSRGS** (TRPV4); **VSRME** (GNAO); **VSYVV** (ADCY6); **VTLGA** (PRAX); **VVAEE** (CXBI; GPR6); **VVDGD** (MYO1D); **VVDPI** (RPC1); **VVGLL** (GDAPI); **YISTR** (STXB1); **YLSTQ** (ACATN); **YSLMA** (ANAG)

Abbreviation: ZIKV, Zika virus.

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