



Case Report Guillain–Barré Syndrome in COVID-19—The Potential Role of NCAM-1 and Immunotherapy

Krzysztof Laudanski ^{1,*}^(D), Aleksandra Yakhkind ²^(D), Mariana Restrepo ³, Lindsay Draham ⁴^(D) and Adam Edward Lang ⁵^(D)

- ¹ Department of Anesthesia and Critical Care, University of Pennsylvania, Philadelphia, PA 19104, USA
- ² Department of Neurology, University of Pennsylvania, Philadelphia, PA 19104, USA; aleksandra.yakhkind@gmail.com
- ³ College of Arts and Sciences, University of Pennsylvania, Philadelphia, PA 19104, USA; rmariana@sas.upenn.edu
- ⁴ Department of Neurosurgery and Neuro Critical Care, University of Pennsylvania, Philadelphia, PA 19104, USA; lindsay.draham@pennmedicine.upenn.edu
- ⁵ Department of Primary Care, McDonald Army Health Center, Fort Eustis, VA 23604, USA; a.edward.lang@gmail.com
- * Correspondence: klaudanski@gmail.com

Abstract: Coronavirus disease 2019 (COVID-19) interacts with the nervous system directly and indirectly by affecting the activation of the immune system. Guillain–Barré syndrome (GBS) is triggered by an inappropriate immune system activation that overlaps with the neurotoxic mechanism of an invading pathogen. Here, we discuss the complexity of an abnormal immune system response leading to the generation of autoimmunity in the setting of acute viral infection. A 67-year-old male patient with COVID-19 developed a sensory motor acute polyneuropathy with respiratory failure. Several serum inflammatory and neurodegeneration markers were collected during hospital days 1, 3, 8, and 67 and compared to healthy individuals. Neural cell adhesion molecule 1 (NCAM-1) and neurofilament light chain (NfL) values were highly variable when compared to healthy individuals, but not to the reference COVID-19 group. We focused our attention on NCAM-1 as a possible target for antibodies directed at COVID-19 in silico.

Keywords: Guillain–Barré syndrome; COVID-19; biomarkers; inflammation; NCAM-1; NF-L; tau protein; critical care illness

1. Introduction

Guillain–Barré syndrome (GBS) is a relatively uncommon condition characterized by an acute onset of muscle weakness and/or sensory loss as a result of a disruption in peripheral nerve myelin and axonal function by the body's immune system [1,2]. The symptoms may progress to respiratory failure, loss of deep tendon reflexes, and dysautonomia. The most common variant is an acute inflammatory demyelinating polyneuropathy, which is characterized by motor weakness, paresthesia and loss of deep tendon reflexes. Less common variants are acute motor and sensory axonal neuropathies, which involve motor and sensory loss, respectively, and characteristic patterns in electromyography and nerve conduction studies (EMG/NCS). While GBS is a clinical syndrome, the following ancillary testing may be supportive of the diagnosis. Cerebrospinal fluid (CSF) analysis often shows albumin-cytologic dissociation in over half of patients, and magnetic resonance imaging of the spinal cord may show nerve root thickening and enhancement [3]. EMG demonstrates a pattern of either demyelinating or axonal polyneuropathy and is more sensitive weeks after the acute phase of illness [3–5].



Citation: Laudanski, K.; Yakhkind, A.; Restrepo, M.; Draham, L.; Lang, A.E. Guillain–Barré Syndrome in COVID-19—The Potential Role of NCAM-1 and Immunotherapy. *BioMed* 2021, *1*, 80–92. https:// doi.org/10.3390/biomed1010006

Academic Editor: Nadia Lampiasi

Received: 20 August 2021 Accepted: 10 September 2021 Published: 15 September 2021

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1.1. Models of Pathophysiology

GBS often follows infection, vaccination, exposure to certain chemicals, or a nonspecific insult to the body due to abnormal immunological response and leads to the generation of autoimmunity (Figure 1A–D) [1,3,4,6]. One of the most prevalent types of GBS is linked to autoantibodies, but antibodies to peripheral nerve gangliosides are detected in only detected in a proportion of patients (Figure 1B) [7]. Several other nodallocated targets have been identified [8]. Cytotoxic T cells and monocytes may also partake in damaging the peripheral nerves. Inappropriate resolution of inflammation in the immunologically privileged nervous system is another potential culprit (Figure 1A). Some of these patients suffer from alternative mechanisms of GBS induction, including the acquisition of immunity secondary to the release of danger signals acting as haptens for the emergence of autoantibodies (Figure 1B) [9,10]. It is also possible that some GBS-like cases represent non-specific nerve damage with GBS-like symptoms (Figure 1E) [11]. Patients with coronavirus disease 2019 (COVID-19) may suffer from a superimposing infection triggering an autoimmune disease, which is GBS (Figure 1B–D) [2]. Finally, other peripheral demyelinating diseases may emerge as they target alternative epitopes and peripheral nerve nodal targets [3,12].



Figure 1. GBS may emerge as a failure of the immune system to eliminate autoreactive B or T cell clones. (**A**) A resemblance of the offending antigen to autoantibodies, (**B**) the inappropriate resolution of inflammation, (**C**) a direct and indirect SARS-CoV-2 effect, (**D**) other diseases resembling GBS, (**E**) a co-infection setting new process in place leading to GBS (**F**).

1.1.1. Molecular Mimicry

Certain features of sudden acute respiratory syndrome coronavirus 2 are neutropic in nature, pointing to the direct contribution of this pathogen to nervous system injury or intrathecal production of autoantibodies [2,13,14].

Autoantibodies are created due to the ongoing release of danger signals from affected neurons, or the presence of virus triggers molecular mimicry. At the same time, the virus triggers immune system activation that potentially results in additional collateral damage, including that of peripheral nerves leading to a potential overlap in the symptoms [15]. What is unclear is if there are specific markers, or inciters, of peripheral nerve damage caused by COVID-19 compared to the those of a viral-induced GBS, or rather a specific cluster for COVID-19-related GBS [16,17].

1.1.2. Inflammation

The onset and progression of GBS has previously been related to certain neuroinflammation characteristics of well-studied neurological disorders [3]. The release of peripheral injury markers seems to be a natural consequence of the autoantibody binding, intrathecal immune system activation, or cytotoxicity [3,18]. While certain markers such as apolipoprotein E (ApoE) seem to be found in decreased levels in patients' CSF, both the plasma and CSF levels of others (interleukin 37 (IL-37), interleukin 17A (IL-17A), interferon gamma $(IFN-\gamma)$, and tumor necrosis factor alpha $(TNF-\alpha)$) seem to be significantly higher following the onset of GBS symptoms [19,20]. This suggests that inflammation may be generalized, therefore distinguishing if the axonal injury is a primary or secondary event. Because many of these markers are indicators of neurological damage, their presence and correlation to COVID-19 patients may provide insight as to how the body immunologically responds to viral infections. The similarities, or distinguishing factors, between these neurodegeneration markers and those seen in central neurodegenerative disorders can therefore be compared to investigate the autoimmune component of COVID-19. Such a comparison must be made with caution, as several markers are somewhat arbitrarily assigned to the central or peripheral part of the nervous system (Table 1).

Table 1. Neurodegeneration, neuroinflammation, and general inflammatory markers and their role in critical care illness and COVID-19. All values are presented in units of pg/mL.

Biomarker		1	Blood		CSF	Reference Ranges	General Description	
	T1	T2	T3	T4			Relevance to COVID-19	
KLK6	923.7	3953.6	3442.7	465.2	14,849.4	unknown	Serum protease, neuroinflammation, linked to multiple sclerosis (MS), elevated in Alzheimer's disease (AD) when tau also elevated, decreased in Parkinson's disease (PD), degraded in respiratory disease, regulates myelin volume. No association with GBS or COVID-19 [21]	
Amyloid B1-41	BDL	BDL	BDL	BDL	BDL	unknown	Was not found in the literature [22]	
Amyloid B1-42	4.2	7.8	12.6	16.1	29.3	0-400 pg/mL (SIMOA)	Lower in AD, no relation to COVID-19 found [22]	
TOT TAU	BDL	121.7	BDL	114.1	BDL	100–300 in GBS, 0–360 pg(SIMOA)	Higher values associated with worse prognosis in GBS [22–26] Also called CD56, helps	
NCAM-1	57,758.5	51,593.3	57,231.2	119,018.3	22,356.6	246.03 pg/mL control, 153 in autism	synapse formation, found to be low in autism, high in MS, hypothetically associated with COVID-19 pathogenesis [27–30]	
TAU PT181	BDL	BDL	BDL	BDL	BDL	unknown	Another marker for tau, no association found with GBS or COVID-19 [23,24]	
TDP43	ND	4045.3	1620.1	5583.8	BDL	unknown	Elevated in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), not GBS. No association with COVID-19 seen [5]	
NFL	41.85	93.15	38.61	192.9		unknown	Elevated in AD, GBS, and ALS, in addition to non-survivors of COVID-19 [31–33]	
NRGN	6052.2	11,867.6	5743.6	11,040.7	1048.9	unknown	Neurogranin: decreased in schizophrenia, increased in AD, no association found with COVID-19 or GBS [23]	
FGF21	BDL	BDL	BDL	BDL	BDL	unknown	Neuroprotectant, involved in carbohydrate metabolism, no link with GBS or COVID [34]	

D ' 1			Blood		CSF	Reference Ranges	General Description
Biomarker	T1	T2	T3	T4			Relevance to COVID-19
CLUSTERIN	11,039.5	1673.9	28,787,864.31	56,444,777.02	29,957.99667	unknown	Increased in AD, no evidence for role in GBS or COVID-19 [35]
TREM2	109.5	144.6	286.51	1833.17	728.849106	unknown	Associated with a risk for AD, can suppress inflammation but also trigger it, no clear association with GBS or COVID-19 [36]
BLC	325.1	6462.4	155.89	200.75	BDL	unknown	B lymphocyte chemoattractant. Associated with adenocarcinoma. Also called CXCL13 or BCA-1. Other types but not this type associated with GBS [37]
YKL40	8684.5	14,853.5	17,258.11	18,389.31	15,090.6293	healthy: 80 ng/mL, severe COVID 300	Also called chitinase-3-like protein 1 (CHI3L1), elevated in AD, not GBS, associated with worse mortality in lung COVID-19 disease [38,39] Binds to pro-inflammatory
RAGE	146.3	124.8	67.87	61.70	24.0432183	serum pg/mL AIDP > 1000, AMAN < 1000	pathways, higher in neurodegenerative disease, lower in AMAN subtype of GBS, higher in AIDP, higher in asymptomatic COVID-19, lower in severe COVID-19 in
FERRITIN	383,593.2	207,231.3	218,048.4	709,040.7	51,863.9	unknown	enzyme-inked immunosorbent assay in ng/mL [2,10,40–42] Increased levels seen in patients that showed inflammation during episode of malaria and COVID-19. Similar results were seen in a patient who presented with GBS associated with COVID-19 [43–45]
DDIMER	110,928.0	34,814.4	25,904.3	6,737,038.6	720,348.9	unknown	Elevated d-dimer plasma levels are associated with inflammatory reactions to pneumonia and severe COVID-19. No association with GBS [46]
IL-6	1.6	22.8	5.0	0.7	<1.04736328125	unknown	increased activation of serum IL-6, similarly to how its role in a "cytokine storm" has been correlated with critical COVID-19 development. It plays both a pro-inflammatory and protective role in
TNF-α	0.0	0.5	0.0	0.0	0.1	unknown	GBS [47,48] Gene polymorphisms prevent efficacious immune response against viruses such as hepatitis B and predict susceptibility to GBS, while decreased levels due to antibiotics (azithromycin specifically) are seen in COVID-19 patients [49]

Table 1. Cont.

Exploring the intricacy of the nervous system is a critical component in completely understanding the interaction between SARS-CoV-2 and the immune system in the emergence of GBS. To begin, the nervous system contains immunologically privileged organs with a tightly regulated entry of leukocytes [50]. To a certain degree, this is also the case for the peripheral nervous system. These immunological properties result in difficulties in

translating the immunological response outside the nervous system to pathologies within the nervous system. Therefore, it is virtually impossible to discern if GBS is triggered by direct viral toxicity or if a viral infection can result in an abnormal immune system activation leading to GBS. It is unknown if the pathological reaction originates in or is driven from the inside or outside of the protected nervous system. The latter is an important point as the traditionally considered protective space of the nervous system may have a role in forming the autoimmune GBS pathology due to an inability to formulate an effective, self-extinguishing resolution of the immune system activation [51,52]. The intersection between COVID-19 and GBS may provide insight as to how the nervous system responds to viral illness and critical care illnesses.

1.2. Correlation with COVID-19

Case reports and case series have described GBS as a complication of COVID-19 with an incidence rate of 47.9 cases/100,000 [2,40,53–57], with the incidence rate in the general population being 1 to 2 cases/100,000 [58]. The comorbidity of COVID-19 and GBS was related to longer hospital stays and increased ICU utilization, but it is unclear if the effects are additive, synergistic, or even different from those in other ICU-related illnesses [11,57]. Reported incidence of GBS increased in 2020 compared to years prior, concomitantly with COVID-19 cases. While this could be due to an increase in reporting, attention to this association could help improve the understanding of both GBS and COVID-19. In essence, this is the conundrum behind the rise of GBS in 2020 and 2021: Is the GBS specific to COVID-19, or does it follow a global trend in mortality due to the bystander effect?

The incidence of GBS in other viral diseases suggests a possible association between GBS and COVID-19. The development of the Zika virus infection in South America, particularly in Colombia and Brazil, has been significantly correlated to the onset and progression of GBS in patients [59]. GBS has also been associated with less prominent viruses such as the Epstein–Barr and hepatitis E viruses [60,61]. In regard to COVID-19, reports have varied as a group of researchers from the United Kingdom report no association between these two illnesses, while others hypothesis a more causal relationship [2,55,62,63]. The relationship between COVID-19 and GBS seems to be elusive in terms of characterizing which one is primary and how specific GBS symptoms are for COVID-19.

We would like to provide a brief review of the current state of this gap in knowledge using a case report to illustrate the complex interaction between COVID-19 and GBS. Furthermore, this case report offers a unique opportunity to evaluate several inflammatory and neuronal injury markers in blood and cerebrospinal fluid longitudinally. This is an illustrative case discussing the role of different types of immune system responses to COVID-19, and infection in general, in the emergence of autoimmunity against the nervous system component. We examined the state of knowledge in respect to markers of neuronal injury in relation to GBS as opposed to other neurodegenerative illnesses. Finally, we would like to highlight the role of neural cell adhesion molecule 1 (NCAM-1) as a potential culprit in sensitizing the immune system to myelin and the subsequent emergence of GBS symptoms.

2. Case Presentation

2.1. Methods

Blood and medical records were examined under the IRB-approved protocol (#843311). Blood was collected in heparin vacutainer tubes (BD, Franklin Lakes, NJ, USA) and put on ice. Serum was separated by collecting the top layer after spinning the line at $1000 \times g$, 10 min, $4 \,^{\circ}\text{C}$ within 3 h from collection. Aliquoted serum was stored at $-80 \,^{\circ}\text{C}$. CSF was collected into standard collection tubes and immediately brought to $-80 \,^{\circ}\text{C}$. The serum was inactivated by incubation of $100 \,\mu\text{L}$ of serum with 5% Tween-20 (Bioworld, Baltimore, MD, USA) for 20 min at room temperature and then analyzed using multiplex assay (Thermo Fisher, Waltham, MA, USA). The biological markers were measured using the multiplex technique and are presented as normalized protein expression (NPX) dimensionless values plotted against protein concentration (pg/mL).

2.2. Case Report

A 67-year-old male presented with three days of ascending numbness and weakness in his hands and feet along with difficulty walking. Exams revealed proximal more than distal weakness with distally diminished sensation in a stocking-glove pattern and absent lower extremity reflexes. His medical history included hypertension, glaucoma, and obstructive sleep apnea. He denied any recent fever, chills, headache, chest pain, abdominal pain, nausea, vomiting, diarrhea, constipation, leg swelling, or trauma. He had not received his flu vaccine that year, and his only new medication was loratadine that he started two weeks prior. He developed a productive cough with clear sputum on the day before admission associated with some shortness of breath. He was afebrile on presentation with tachycardia and normal oxygen saturation of 97% in room air. Initial laboratory workup revealed only elevated C-reactive protein (29.1 mg/L) and sedimentation rate (103 mm/h). His anti-ganglioside antibody panel, myelin oligodendrocyte glycoprotein antibodies, and anticholinergic antibodies were negative, but the nasopharyngeal SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) swab returned positive twice.

Negative inspiratory force of $-10 \text{ cmH}_2\text{O}$ prompted transfer to the intensive care unit. Considering no fevers, infiltrates on chest X-ray, or other lab abnormalities suggested severe COVID-19 treatment, dexamethasone or remdesivir were deferred. He had weak bilateral hand grip, no movement in bilateral lower extremities, intact sensation and proprioception throughout, and absent reflexes except in bilateral wrist extensors. His respiratory strength declined, and he required bilevel positive airway pressure ventilation (day 2) and intubation (day 3) (Figure 2) [18]. Cervical, thoracic, and lumbar spine magnetic resonance imaging was completed on day 4 and revealed no definite leptomeningeal, spinal cord, or nerve root enhancement. Lumbar puncture performed on day 4 revealed an opening pressure of 27 cmH₂O, CSF protein of 117 mg/dL (normal 15–45 mg/dL), CSF white blood cells of $2/\mu$ L (normal 0–5/ μ L), and 115/ μ L red blood cells (normal 0/ μ L).



Figure 2. Clinical trajectory of the patient.

Plasmapheresis (PLEX) was initiated on day 3 [18]. Intravenous immunoglobulins were thought to have a theoretical contraindication in the setting of possible hypercoagulability due to COVID-19. The benefits of PLEX were determined to outweigh the risks of immunosuppression given his rapid neuromuscular respiratory failure and profound weakness. Despite five PLEX sessions (days 3, 5, 7, 9, and 11 of hospital stay), his exam continued to worsen to only nodding and intact shoulder shrug, but also facial diplegia, quadriplegia, and severe dysautonomia. On day 17, needle EMG/NCS examination revealed moderate to severe sensorimotor polyneuropathy with features of axonal degeneration. Repeated EMG/NCS on day 31 revealed continued evidence of severe axonal sensorimotor polyneuropathy. The patient was ultimately transferred to a ventilator weaning facility on day 40 of his hospital course. He was liberated from the ventilator on day 61 and transferred to an acute rehabilitation facility (day 85) and home (day 112). At this time, he remained wheelchair-bound with no sensation in his ankles and feet, but able to perform his activities of daily living with minimal assistance.

Serum levels of spike protein and anti-SN antibodies followed the expected clinical trajectory, with initial increase of antigen (S-spike) and IgG following it (Figure 3A). The level of inflammatory response was signified by ferritin, d-dimer, and a brief spike of serum IL-6 (Table 1). Analysis of biomarkers demonstrated an elevation in NCAM-1, no changes in phosphorylated tau or amyloid β -1–40, and some fluctuation in NfL (Figure 3B).



Figure 3. Changes in spike protein and reactive antibodies followed expected trajectory (**A**), but NCAM-1 continued to increase as compared to tau protein (**B**).

2.3. Clinical Presentation Discussion

The presented case of GBS is a hallmark of several conundrums when debating GBS in the context of COVID-19. The patient's initial presentation was strictly neurologic in nature, eventually worsening to respiratory failure as seen in classic severe GBS. Lack of clear antibodies while presenting with the classic symptoms of GBS demonstrates difficulty in judging the etiology of the disease, hampers the treatment, and potentially casts doubt on the accuracy of diagnosis. Furthermore, lack of a response to plasmapheresis suggests that the neurological symptoms were not antibody mediated, as plasmapheresis removes immunoglobulin and serum inflammatory mediators. Instead, the patient may experience a cytotoxic-based response leading to an attack on the peripheral ceramide, myelin, or potentially other targets. In addition, the patient's IL-6 response was quite subdued despite other markers (C-reactive protein, ferritin) being severely elevated [64]. IL-6 is frequently received as danger signal and culprit of organ damage in critical care illnesses [65]. However, it is also necessary for immunoglobulin switching, a critical part of the optimal response. Consequently, one would expect it to be elevated. The nature of cytotoxic response is mediated by direct cell-to-cell contact and executed by cytotoxic T cells, natural killer cells, and sensitized monocytes. This is only an assumption as no specific test exists to evaluate cellular autoreactivity in the case of GBS.

There is also still uncertainty regarding whether the patient had another viral infection that had become symptomatic, if the patient was sensitized secondary to an unknown exposure, or rather if the subsequent worsening of symptoms was secondary to COVID-19 or the worsening respiratory failure from the muscle weakness itself. This patient's EMG demonstrated the typical findings of GBS, yet it is possible that the patient suffered from superimposed axonal damage, or critical care illness polyneuropathy.

The patient received several treatments with PLEX. The therapy should lower the levels of antibodies, but its response is highly erratic. Furthermore, there are no directly linear relationships between antibodies and the severity of symptoms previously studied. While immunoglobulins have previously been used in the treatment of COVID-19 patients experiencing GBS, none were used in this case [56]. The patient focused on in this study showed both increased immunoglobulin G and A levels from the first to the last collection timepoints and therefore did not demonstrate a need for intravenous immunoglobulins (data not shown). A causal relationship between immunoglobulin levels, COVID-19, and GBS may be problematic as even though no other pathogens were detected in the patient, they cannot be ruled out.

The plethora of neurological biomarker abnormalities present during the observed case illustrates the difficulty in distinguishing between non-specific inflammatory response versus viral infection from COVID-19 mediated mechanisms leading to GBS. We detected elevation of tau, amyloid X, and NfL levels. Phosphorylated tau was not detected. However, the assays used may not have been sensitive enough to record these markers. Several markers typical to neurodegenerative disorders, including Alzheimer's disease, were elevated. This observation is consistent with acute brain injury and secondary to either direct neurotoxic effects or inflammatory response in the brain. Some have suggested an interaction between COVID-19 and the abnormal activation of several phosphorylation neurodegeneration pathways, but it is also likely that the elevation in markers is secondary to injury due to critical care illness.

3. Discussion

The presented case of GBS is a hallmark of several conundrums when debating GBS in the context of COVID-19. It is impossible to tell if the emergence of GBS symptoms was related to COVID-19 exclusively. The patient could have suffered from another viral or bacterial disease even though extensive testing failed to detect one. It seems that the level of immunological response to COVID-19 did not correlate with the severity of the disease. This suggests that clinical symptoms of GBS were initiated but not sustained by COVID-19. In that case, COVID-19 follows a similar trajectory as seen in other viral-triggered GBS.

cases [59,66–68]. For the discussion, we are in favor of diagnosing this patient with GBS based on clinical studies.

The elevation of serum neuroinflammation markers in the early stages of COVID-19 may reflect the beginning of neurological damage, whether it be acute or chronic. Increased levels of neuroprotective markers in the later stages may possibly prevent neurodegeneration as they subdue the virus' attack (Figure 3).

NCAM-1 as a Potential Link between GBS and COVID-19

The activation of the immune system, measured via changes in inflammatory markers, is part of a generalized response. It is unclear how this would lead to a case of GBS except via severely deranged immunity leading to non-specific nerve damage processes initiated by the exposure of the immune system to the antigen on the surface of peripheral nerves, triggering antibody production or cytotoxic cellular response. The trigger for the emergence of autoimmunity may have several origins. Circulating products of inflammation and cellular damage secondary to sepsis may function as haptens, rendering previously harmless molecules immunologically active [10,41]. The receptor for the advanced glycation endproducts (RAGE) pathway was suggested to be one of the culprits. The autoimmune system may activate secondary to molecular mimicry. In classical GBS, ganglioside antibodies may be formed due to exposure to several lookalike molecules, although molecular mimicry may play a role in other presentations of GBS when autoantibodies emerge directed at other targets due to a similar mechanism. In fact, Devaux et al. demonstrated several nodal targets with some mimicry to anti-GM antibodies [8]. Gliomedin, contactin, and NCAM were shown to trigger the increase in autoantibodies. Neurofascin is another potential target leading to the emergence of peripheral autoimmune neuropathy [12].

Consequently, of interest is which of the autoantibodies are predominantly responsible for symptoms typical of GBS. Devaux et al. also suggested that anti-GM antibodies can be triggered secondary to primary processes and alternative targets. Once anti-GM antibodies emerge, then patients demonstrate clinical symptoms for GBS or other peripheral demyelinating diseases [8].

Interestingly, in silico, NCAM was found to be 85% identical to SARS-CoV-2 envelope proteins, suggesting that an immune response against SARS-CoV-2 could theoretically create antibodies against NCAM and lead to demyelination and polyneuropathy [69]. Furthermore, most patients in the largest case series of GBS and COVID-19 had negative anti-ganglioside antibodies like our patient, suggesting another culprit at play [70]. The level of NCAM-1 fluctuated significantly, consistent with the previously observed elevation of markers in the setting of muscle denervation which has been implicated as an antibody target in acute polyneuropathies [8,12]. In a subgroup of GBS patients, antibodies to NCAM-2 were detected, but NCAM-1 itself was not measured [69]. NCAM-1 has been identified as a possible target for antibodies directed at COVID-19 in silico, possibly playing a role in the demyelination and polyneuropathy seen in this patient [69]. This finding is a first step to understanding the molecular underpinnings of the relationship between COVID-19 and the peripheral nervous system.

The potential mimicry of SARS-CoV-2 envelope proteins and NCAM-1 is not the only one described in the literature. Considering certain similarities between COVID-19, vasculitis, and autoimmune disease, some suggested that molecular mimicry may play a very significant role in the pathology of COVID-19 comorbidities. Release of danger signals, in particular heat shock protein, can acquire the antigen features by self-proteins [70]. Increased support for this hypothesis is provided by homology between viral protein sequence and respiratory pacemaker neuron proteins [71]. Consequently, COVID-19 may result in acquisition of reactivity to existing self-antigens by the host. A review of the auto-epitope antibodies database revealed several other potential targets [72,73]. COVID-19 can also exacerbate pre-existing autoimmune disorders, especially ones with mimicry such as ankylosis spondylosis [74]. It is unclear if this process is specific to autoantibodies

emerging in response to COVID-19 or if it is a generalized response to viral infections in particular [27,72,75].

In silico modeling to narrow down the list of potential targets is being utilized with increasing frequency. COVID-19 provides a new impetus to the process that was already quite mature. In general, modeling should allow for the generation of the best fit in a timely fashion. Though the translation is still missing, the new impetus provided by COVID-19 will allow an understanding of how in silico modeling can help verify experimental observation, generate new leads, or limit possible hypotheses down to the most promising [76]. In the case of GBS and NCAM-1, a promising lead has been suggested, yet it has to be actionable.

4. Conclusions

The relationship between COVID-19 and GBS seems to be similar to those observed in other viral diseases. This theoretical report suggests possible molecular mimicry between NCAM-1 and the SARS-CoV-2 envelope protein.

Author Contributions: Concept—K.L.; Data Collection—K.L., A.E.L., A.Y.; Original Manuscript— M.R., K.L.; Final Review—K.L., A.Y., M.R., L.D., A.E.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the University of Pennsylvania (#843311; approved on 6 February 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available upon reasonable request pending University of Pennsylvania IRB release.

Conflicts of Interest: The authors declare no conflict of interest. The views expressed in this publication are those of the authors and do not necessarily reflect the official policy of the Department of Defense, Department of the Army, U.S. Army Medical Department, or the U.S. Government.

Abbreviations

Kallikrein-6
Total tau protein
Neural cell adhesion molecule 1
TAR DNA-binding protein 43
Neurofilament light chain
Neurogranin
Fibroblast growth factor 21
Triggering receptor expressed on myeloid cells 2
B lymphocyte chemoattractant
Chitinase-3-like protein 1
Receptor for advanced glycation endproducts
Tumor necrosis factor alpha
Acute motor axonal neuropathy
Acute inflammatory demyelinating polyneuropathy
Coronavirus disease 2019
Guillain–Barré syndrome
Cerebrospinal fluid
Apolipoprotein E
Interleukin 37
Interleukin 17A
Interferon gamma
Severe acute respiratory syndrome coronavirus 2

CRP	C-reactive protein
RT-PCR	Reverse transcription polymerase chain reaction
PLEX	Plasmapheresis
EMG	Electromyography
IgG	Immunoglobulin G
IL-6	Interleukin 6
MS	Multiple sclerosis
AD	Alzheimer's Disease
PD	Parkinson's Disease
ALS	Amyotrophic lateral sclerosis
FTD	Frontotemporal dementia

References

- 1. Dimachkie, M.M.; Barohn, R.J. Guillain-Barré syndrome and variants. Neurol. Clin. 2013, 31, 491–510. [CrossRef]
- 2. Diez-Porras, L.; Vergés, E.; Gil, F.; Vidal, M.J.; Masson, J.; Arboix, A. Guillain-Barré-Strohl syndrome and COVID-19: Case report and literature review. *Neuromuscul. Disord.* **2020**, *30*, 859–861. [CrossRef]
- 3. Saporta, M.A.; Shy, M.E. Chapter 12—Peripheral neuropathies. In *Neurobiology of Brain Disorders*; Zigmond, M.J., Rowland, L.P., Coyle, J.T., Eds.; Academic Press: San Diego, CA, USA, 2015; pp. 167–188.
- 4. Eldar, A.H.; Chapman, J. Guillain Barré syndrome and other immune mediated neuropathies: Diagnosis and classification. *Autoimmun. Rev.* 2014, *13*, 525–530. [CrossRef]
- De Boer, E.M.J.; Orie, V.K.; Williams, T.; Baker, M.R.; De Oliveira, H.M.; Polvikoski, T.; Silsby, M.; Menon, P.; van den Bos, M.; Halliday, G.M.; et al. TDP-43 proteinopathies: A new wave of neurodegenerative diseases. *J. Neurol. Neurosurg. Psychiatry* 2020, 92, 86–95. [CrossRef]
- 6. Yuki, N.; Hartung, H.P. Guillain–Barré syndrome. N. Engl. J. Med. 2012, 366, 2294–2304. [CrossRef] [PubMed]
- 7. Willison, H.J.; Goodyear, C.S. Glycolipid antigens and autoantibodies in autoimmune neuropathies. *Trends Immunol.* **2013**, *34*, 453–459. [CrossRef] [PubMed]
- 8. Devaux, J.J.; Odaka, M.; Yuki, N. Nodal proteins are target antigens in Guillain-Barré syndrome. *J. Peripher. Nerv. Syst.* 2012, 17, 62–71. [CrossRef] [PubMed]
- Erkes, D.A.; Selvan, S.R. Hapten-induced contact hypersensitivity, autoimmune reactions, and tumor regression: Plausibility of mediating antitumor immunity. J. Immunol. Res. 2014, 2014, 1755265. [CrossRef]
- 10. Yalcin Kehribar, D.; Cihangiroglu, M.; Sehmen, E.; Avci, B.; Capraz, A.; Yildrim Gilgin, A.; Gunaydin, C.; Ozgen, M. The receptor for advanced glycation end product (RAGE) pathway in COVID-19. *Biomarkers* **2021**, *26*, 114–118. [CrossRef]
- 11. Inoue, S.; Hatakeyama, J.; Kondo, Y.; Hifumi, T.; Sakuramoto, H.; Kawasaki, T.; Taito, S.; Nakamura, K.; Unoki, T.; Kawai, Y.; et al. Post-intensive care syndrome: Its pathophysiology, prevention, and future directions. *Acute Med. Surg.* **2019**, *6*, 233–246. [CrossRef]
- 12. Delmont, E.; Manso, C.; Querol, L.; Cortese, A.; Berardinelli, A.; Lozza, A.; Belghazi, M.; Malissart, P.; Labauge, P.; Taieb, G.; et al. Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. *Brain* **2017**, 140, 1851–1858. [CrossRef] [PubMed]
- 13. Lewis, A.; Frontera, J.; Placantonakis, D.G.; Lighter, J.; Galetta, S.; Balcer, L.; Melmed, K.R. Cerebrospinal fluid in COVID-19: A systematic review of the literature. *J. Neurol. Sci.* 2021, 421, 117316. [CrossRef] [PubMed]
- Guadarrama-Ortiz, P.; Choreño-Parra, J.A.; Sánchez-Martínez, C.M.; Pacheco-Sánchez, F.J.; Rodríguez-Nava, A.I.; García-Quintero, G. Neurological Aspects of SARS-CoV-2 Infection: Mechanisms and Manifestations. *Front. Neurol.* 2020, *11*, 1039. [CrossRef] [PubMed]
- Kajumba, M.M.; Kolls, B.J.; Koltai, D.C.; Kaddumukasa, M.; Kaddumukasa, M.; Laskowitz, D.T. COVID-19-Associated Guillain-Barre Syndrome: Atypical Para-infectious Profile, Symptom Overlap, and Increased Risk of Severe Neurological Complications. SN Compr. Med. 2020, 1–13. [CrossRef]
- 16. Wang, X.K.; Zhang, H.L.; Meng, F.H.; Chang, M.; Wang, Y.Z.; Jin, T.; Mix, E.; Zhu, J. Elevated levels of S100B, tau and pNFH in cerebrospinal fluid are correlated with subtypes of Guillain–Barré syndrome. *Neurol. Sci.* **2013**, *34*, 655–661. [CrossRef]
- 17. Gigli, G.L.; Bax, F.; Marini, A.; Pellitteri, G.; Scalise, A.; Surcinelli, A.; Valente, M. Guillain-Barré syndrome in the COVID-19 era: Just an occasional cluster? *J. Neurol.* **2021**, *268*, 1195–1197. [CrossRef]
- Shang, P.; Feng, J.; Wu, W.; Zhang, H.L. Intensive Care and Treatment of Severe Guillain-Barré Syndrome. *Front. Pharmacol.* 2021, 12, 608130. [CrossRef]
- 19. Jin, T.; Hu, L.S.; Chang, M.; Wu, J.; Winblad, B.; Zhu, J. Proteomic identification of potential protein markers in cerebrospinal fluid of GBS patients. *Eur. J. Neurol.* 2007, 14, 563–568. [CrossRef]
- 20. Li, C.; Zhao, P.; Sun, X.; Che, Y.; Jiang, Y. Elevated levels of cerebrospinal fluid and plasma interleukin-37 in patients with Guillain-Barré syndrome. *Mediat. Inflamm.* **2013**, 2013, 639712. [CrossRef]
- 21. Mella, C.; Figueroa, C.D.; Otth, C.; Ehrenfeld, P. Involvement of Kallikrein-Related Peptidases in Nervous System Disorders. *Front. Cell. Neurosci.* **2020**, *14*, 166. [CrossRef]

- 22. Lue, L.F.; Guerra, A.; Walker, D.G. Amyloid Beta and Tau as Alzheimer's Disease Blood Biomarkers: Promise from New Technologies. *Neurol. Ther.* 2017, *6*, 25–36. [CrossRef] [PubMed]
- Mattsson, N.; Insel, P.S.; Palmqvist, S.; Portelius, E.; Zetterberg, H.; Weiner, M.; Blennow, K.; Hansson, O. Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. *EMBO Mol. Med.* 2016, *8*, 1184–1196. [CrossRef] [PubMed]
- Rubenstein, R.; Chang, B.; Yue, J.K.; Chiu, A.; Winkler, E.A.; Puccio, A.M.; Diaz-Arrastia, R.; Yuh, E.L.; Mukherjee, P.; Valadka, A.B.; et al. Comparing Plasma Phospho Tau, Total Tau, and Phospho Tau-Total Tau Ratio as Acute and Chronic Traumatic Brain Injury Biomarkers. *JAMA Neurol.* 2017, 74, 1063–1072. [CrossRef] [PubMed]
- 25. Asbury, A. CSF tau protein: A new prognostic marker for Guillain-Barre syndrome. Neurology 2007, 68, 1438–1439. [CrossRef]
- 26. Jin, K.; Takeda, A.; Shiga, Y.; Sato, S.; Ohnuma, A.; Nomura, H.; Arai, H.; Kusunoki, S.; Ikeda, M.; Itoyama, Y. CSF tau protein: A new prognostic marker for Guillain-Barré syndrome. *Neurology* **2006**, *67*, 1470–1472. [CrossRef] [PubMed]
- Lucchese, G.; Flöel, A.; Stahl, B. Cross-Reactivity as a Mechanism Linking Infections to Stroke. *Front. Neurol.* 2019, 10, 469. [CrossRef] [PubMed]
- Ziliotto, N.; Zivadinov, R.; Jakimovski, D.; Baroni, M.; Tisato, V.; Secchiero, P.; Bergsland, N.; Ramasamy, D.P.; Weinstock-Guttman, B.; Bernardi, F.; et al. Plasma levels of soluble NCAM in multiple sclerosis. J. Neurol. Sci. 2019, 396, 36–41. [CrossRef]
- Yang, X.; Zou, M.; Pang, X.; Liang, S.; Sun, C.; Wang, J.; Fan, L.; Xia, W.; Wu, L. The association between NCAM1 levels and behavioral phenotypes in children with autism spectrum disorder. *Behav. Brain Res.* 2019, 359, 234–238. [CrossRef]
- 30. Sytnyk, V.; Leshchyns'ka, I.; Schachner, M. Neural Cell Adhesion Molecules of the Immunoglobulin Superfamily Regulate Synapse Formation, Maintenance, and Function. *Trends Neurosci.* **2017**, *40*, 295–308. [CrossRef]
- 31. Gaetani, L. Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg, H. Neurofilament light chain as a biomarker in neurological disorders. J. Neurol. Neurosurg. Psychiatry 2019, 90, 870–881. [CrossRef]
- 32. Gaiottino, J.; Norgren, N.; Dobson, R.; Topping, J.; Nissim, A.; Malaspina, A.; Bestwick, J.P.; Monsch, A.U.; Regeniter, A.; Lindberg, R.; et al. Increased neurofilament light chain blood levels in neurodegenerative neurological diseases. *PLoS ONE* **2013**, *8*, e75091.
- Aamodt, A.H.; Høgestøl, E.A.; Popperud, T.H.; Holter, J.C.; Dyrhol-Riise, A.M.; Tonby, K.; Stiksrud, B.; Quist-Paulsen, E.; Berge, T.; Barratt-Due, A.; et al. Blood neurofilament light concentration at admittance: A potential prognostic marker in COVID-19. *J. Neurol.* 2021, 1–10. [CrossRef]
- 34. Chen, S.; Chen, S.T.; Sun, Y.; Xu, Z.; Wang, Y.; Yao, S.Y.; Yao, W.B.; Gao, X.D. Fibroblast growth factor 21 ameliorates neurodegeneration in rat and cellular models of Alzheimer's disease. *Redox Biol.* **2019**, *22*, 101133. [CrossRef]
- 35. Desikan, R.S.; Thompson, W.K.; Holland, D.; Hess, C.P.; Brewer, J.B.; Zetterberg, H.; Blennow, K.; Andreassen, O.A.; McEvoy, L.K.; Hyman, B.T.; et al. The Role of Clusterin in Amyloid-β–Associated Neurodegeneration. *JAMA Neurol.* **2014**, *71*, 180–187. [CrossRef]
- 36. Jay, T.R.; von Saucken, V.E.; Landreth, G.E. TREM2 in Neurodegenerative Diseases. Mol. Neurodegener. 2017, 12, 56. [CrossRef]
- 37. Chiang, S.; Ubogu, E.E. The role of chemokines in Guillain-Barré syndrome. Muscle Nerve 2013, 48, 320–330. [CrossRef] [PubMed]
- 38. Schoneveld, L.; Ladang, A.; Henket, M.; Frix, A.N.; Cavalier, E.; Guiot, J. COVID-19 Clinical Investigators of the CHU de Liège. YKL-40 as a new promising prognostic marker of severity in COVID infection. *Crit. Care* **2021**, *25*, 66. [CrossRef]
- Baldacci, F.; Lista, S.; Cavedo, E.; Bonuccelli, U.; Hampel, H. Diagnostic function of the neuroinflammatory biomarker YKL-40 in Alzheimer's disease and other neurodegenerative diseases. *Expert Rev. Proteom.* 2017, 14, 285–299. [CrossRef] [PubMed]
- 40. Abdullahi, A.; Candan, S.A.; Soysal Tomruk, M.; Elibol, N.; Dada, O.; Truijen, S.; Saeys, W. Is Guillain-Barré Syndrome Associated with COVID-19 Infection? A Systemic Review of the Evidence. *Front. Neurol.* **2021**, *11*, 566308. [CrossRef]
- 41. Zhang, D.Q.; Wang, R.; Li, T.; Zhou, J.P.; Chang, G.Q.; Zhao, N.; Yang, L.N.; Zhai, H.; Yang, L. Reduced soluble RAGE is associated with disease severity of axonal Guillain-Barré syndrome. *Sci. Rep.* **2016**, *6*, 21890. [CrossRef]
- 42. Ray, R.; Juranek, J.K.; Rai, V. RAGE axis in neuroinflammation, neurodegeneration and its emerging role in the pathogenesis of amyotrophic lateral sclerosis. *Neurosci. Biobehav. Rev.* 2016, 62, 48–55. [CrossRef]
- 43. Cheng, L.; Li, H.; Li, L.; Liu, C.; Yan, S.; Chen, H.; Li, Y. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J. Clin. Lab. Anal. 2020, 34, e23618. [CrossRef] [PubMed]
- 44. Namaste, S.M.; Rohner, F.; Huang, J.; Bhushan, N.L.; Flores-Ayala, R.; Kupka, R.; Mei, Z.; Rawat, R.; Williams, A.M.; Raiten, D.J.; et al. Adjusting ferritin concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. *Am. J. Clin. Nutr.* **2017**, *106*, 359s–371s. [PubMed]
- 45. Gagarkin, D.A.; Dombrowski, K.E.; Thakar, K.B.; DePetrillo, J.C. Acute inflammatory demyelinating polyneuropathy or Guillain-Barré syndrome associated with COVID-19: A case report. *J. Med. Case Rep.* **2021**, *15*, 219. [CrossRef] [PubMed]
- Ge, Y.L.; Liu, C.H.; Wang, N.; Xu, J.; Zhu, X.Y.; Su, C.S.; Li, H.L.; Zhang, H.F.; Li, Z.Z.; Li, H.L.; et al. Elevated Plasma D-Dimer in Adult Community-Acquired Pneumonia Patients is Associated with an Increased Inflammatory Reaction and Lower Survival. *Clin. Lab.* 2019, 65. [CrossRef] [PubMed]
- 47. Han, H.; Ma, Q.; Li, C.; Liu, R.; Zhao, L.; Wang, W.; Zhang, P.; Liu, X.; Gao, G.; Liu, F. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg. Microbes Infect.* **2020**, *9*, 1123–1130. [CrossRef]
- 48. Lu, M.O.; Zhu, J. The role of cytokines in Guillain-Barré syndrome. J. Neurol. 2020, 258, 533–548. [CrossRef]
- 49. Ahmadpoor, P.; Rostaing, L. Why the immune system fails to mount an adaptive immune response to a COVID-19 infection. *Transpl. Int.* **2020**, *33*, 824–825. [CrossRef]
- 50. Engelhardt, B. The blood-central nervous system barriers actively control immune cell entry into the central nervous system. *Curr. Pharm. Des.* **2008**, *14*, 1555–1565. [CrossRef]

- 51. Tsygan, N.V.; Trashkov, A.P.; Litvinenko, I.V.; Yakovleva, V.A.; Ryabtsev, A.V.; Vasiliev, A.G.; Churilov, L.P. Autoimmunity in acute ischemic stroke and the role of blood-brain barrier: The dark side or the light one? *Front. Med.* 2019, *13*, 420–426. [CrossRef]
- 52. Javidi, E.; Magnus, T. Autoimmunity after Ischemic Stroke and Brain Injury. Front. Immunol. 2019, 10, 686. [CrossRef] [PubMed]
- 53. Juliao Caamaño, D.S.; Alonso Beato, R. Facial diplegia, a possible atypical variant of Guillain-Barré Syndrome as a rare neurological complication of SARS-CoV-2. *J. Clin. Neurosci.* 2020, 77, 230–232. [CrossRef]
- 54. Toscano, G.; Palmerini, F.; Ravaglia, S.; Ruiz, L.; Invernizzi, P.; Cuzzoni, M.G.; Franciotta, D.; Baldanti, F.; Daturi, R.; Postorino, P.; et al. Guillain-Barré Syndrome Associated with SARS-CoV-2. *N. Engl. J. Med.* **2020**, *382*, 2574–2576. [CrossRef]
- 55. Marta-Enguita, J.; Rubio-Baines, I.; Gastón-Zubimendi, I. Fatal Guillain-Barre syndrome after infection with SARS-CoV-2. *Neurologia* **2020**, *35*, 265–267. [CrossRef] [PubMed]
- 56. Scheidl, E.; Canseco, D.D.; Hadji-Naumov, A.; Bereznai, B. Guillain-Barré syndrome during SARS-CoV-2 pandemic: A case report and review of recent literature. *J. Peripher. Nerv. Syst.* **2020**, *25*, 204–207. [CrossRef] [PubMed]
- 57. Filosto, M.; Cotti Piccinelli, S.; Gazzina, S.; Foresti, C.; Frigeni, B.; Servalli, M.C.; Sessa, M.; Cosentino, G.; Marchioni, E.; Ravaglia, S.; et al. Guillain-Barré syndrome and COVID-19: An observational multicentre study from two Italian hotspot regions. *J. Neurol. Neurosurg. Psychiatry* **2021**, *92*, 751–756. [CrossRef] [PubMed]
- 58. Rinaldi, S. Coronavirus Disease 2019 and the Risk of Guillain-Barré Syndrome. Ann. Neurol. 2021, 89, 846. [CrossRef]
- Parra, B.; Lizarazo, J.; Jiménez-Arango, J.A.; Zea-Vera, A.F.; González-Manrique, G.; Vargas, J.; Angarita, J.A.; Zuñiga, G.; Lopez-Gonzalez, R.; Beltran, C.L.; et al. Guillain-Barré Syndrome Associated with Zika Virus Infection in Colombia. *N. Engl. J. Med.* 2016, 375, 1513–1523. [CrossRef]
- 60. Liu, H.; Ma, Y. Hepatitis E virus-associated Guillain-Barre syndrome: Revision of the literature. *Brain Behav.* **2020**, *10*, e01496. [CrossRef]
- 61. Tam, C.C.; O'Brien, S.J.; Petersen, I.; Islam, A.; Hayward, A.; Rodrigues, L.C. Guillain-Barré syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. *PLoS ONE* 2007, 2, e344. [CrossRef]
- 62. McDonnell, E.P.; Altomare, N.J.; Parekh, Y.H.; Gowda, R.C.; Parikh, P.D.; Lazar, M.H.; Blaser, M.J. COVID-19 as a Trigger of Recurrent Guillain-Barré Syndrome. *Pathogens* **2020**, *9*, 965. [CrossRef] [PubMed]
- 63. Padroni, M.; Mastrangelo, V.; Asioli, G.M.; Pavolucci, L.; Abu-Rumeileh, S.; Piscaglia, M.G.; Querzani, P.; Callegarini, C.; Foschi, M. Guillain-Barré syndrome following COVID-19: New infection, old complication? *J. Neurol.* **2020**, *267*, 1877–1879. [CrossRef]
- 64. Jawa, R.S.; Anillo, S.; Huntoon, K.; Baumann, H.; Kulaylat, M. Interleukin-6 in surgery, trauma, and critical care part II: Clinical implications. *J. Intensive Care Med.* **2011**, *26*, 73–87. [CrossRef]
- 65. Grifoni, E.; Valoriani, A.; Cei, F.; Lamanna, R.; Gelli, A.; Ciambotti, B.; Vannucchi, V.; Moroni, F.; Pelagatti, L.; Tarquini, R.; et al. Interleukin-6 as prognosticator in patients with COVID-19. *J. Infect.* **2020**, *81*, 452–482. [CrossRef] [PubMed]
- Schuler-Faccini, L.; Ribeiro, E.M.; Feitosa, I.M.; Horovitz, D.D.; Cavalcanti, D.P.; Pessoa, A.; Doriqui, M.J.; Neri, J.I.; Neto, J.M.; Wanderley, H.Y.; et al. Possible Association between Zika Virus Infection and Microcephaly—Brazil, 2015. *MMWR Morb. Mortal. Wkly. Rep.* 2016, 65, 59–62. [CrossRef] [PubMed]
- 67. Schmitt, K.; Charlins, P.; Veselinovic, M.; Kinner-Bibeau, L.; Hu, S.; Curlin, J.; Remling-Mulder, L.; Olson, K.E.; Aboellail, T.; Akkina, R. Zika viral infection and neutralizing human antibody response in a BLT humanized mouse model. *Virology* **2018**, *515*, 235–242. [CrossRef]
- Santos, F.R.S.; Nunes, D.A.F.; Lima, W.G.; Davyt, D.; Santos, L.L.; Taranto, A.G.; Ferreira, J.M.S. Identification of Zika Virus NS2B-NS3 Protease Inhibitors by Structure-Based Virtual Screening and Drug Repurposing Approaches. J. Chem. Inf. Model. 2020, 60, 731–737. [CrossRef]
- 69. Morsy, S. NCAM protein and SARS-COV-2 surface proteins: In-silico hypothetical evidence for the immunopathogenesis of Guillain-Barré syndrome. *Med. Hypotheses* **2020**, *145*, 110342. [CrossRef] [PubMed]
- Paladino, L.; Vitale, A.M.; Caruso Bavisotto, C.; Conway de Macario, E.; Cappello, F.; Macario, A.; Gammazza, A.M. The Role of Molecular Chaperones in Virus Infection and Implications for Understanding and Treating COVID-19. *J. Clin. Med.* 2020, *9*, 3518.
 [CrossRef]
- 71. Lucchese, G.; Flöel, A. Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons. *Autoimmun. Rev.* 2020, 19, 102556. [CrossRef]
- 72. Kanduc, D.; Shoenfeld, Y. On the molecular determinants of the SARS-CoV-2 attack. *Clin. Immunol.* 2020, 215, 108426. [CrossRef] [PubMed]
- 73. Vojdani, A.; Kharrazian, D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clin. Immunol.* **2020**, 217, 108480. [CrossRef]
- Guadarrama-Ortiz, P.; Choreño-Parra, J.A.; Pacheco-Sánchez, F.J.; Ponce-Sánchez, J.M.; García-Quintero, G.; Rodríguez-Muñoz, P.E.; Prieto-Rivera, Á.D. Chronic subclinical spondylotic myelopathy exacerbated by COVID-19: A case report. *Interdiscip. Neurosurg.* 2021, 23, 100896. [CrossRef]
- 75. Lucchese, G.; Flöel, A.; Stahl, B. A Peptide Link between Human Cytomegalovirus Infection, Neuronal Migration, and Psychosis. *Front. Psychiatry* **2020**, *11*, 349. [CrossRef] [PubMed]
- Dariolli, R.; Campana, C.; Gutierrez, A.; Sobie, E.A. In vitro and In silico Models to Study SARS-CoV-2 Infection: Integrating Experimental and Computational Tools to Mimic "COVID-19 Cardiomyocyte". *Front. Physiol.* 2021, 12, 624185. [CrossRef] [PubMed]