

POSTINFECTION-POST VACCINATION AUTOIMMUNE NEURAL LONG COVID-19

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Abstract

Normal human subject can have baseline auto-antibodies and auto-reactive immune cells constituting the normal physiological autoimmune state. On, post- sars-cov-2 infection and post-vaccination periods either the virus built in spike protein in case of post-infection . Or the peptide expressed from the spike protein sequence within the human covid -19 mRNA vaccines have an auto-reacting epitopes within the human vaccinee cells. Both of the virus spike protein and vaccinee cells are bearing either pan-sharing molecular mimicking or mono-specific molecular mimicking epitopes that initiate on continual exposure to the immune system cells mediating an autoimmune responses. Such responses may cause an immune conversion of the antibody and /or auto-reactive immune cells levels from the baseline limits to the clinically indicative levels of auto-antibody and/or auto-reacting cells . The immune conversion state may pose to an autoimmune tissue injuries as single or multiple organs defects expressing the patho-biologic features of autoimmune long covid-19.This mechanistic view to the long covid-19 is parallel with inclusion of long covid-19 on the list of autoimmune registry 2021.Some workers holds the believe that autoimmune long covid-19 is an auto-antibody mediated condition .Other workers are of the opinion that both auto-antibody and auto-reacting immune cells may be involved in ,though there is still existing some debate .A literature show case analysis of neural autoimmune long covid-19 was tempted .A laboratory animal model for Post-infection-Post-vaccination autoimmune long covid-19 was suggested .Both of these disease entities are being over-lapping .

Key Words: Autoantibody, Auto-reacting cells,covid-19,epitope,long covid ,tissue injury.

Introduction:

Autoimmune responses [physiological ,pathological] and autoimmune disease conditions[pathological] are an aberrant reactions occurs in human body at most in two cases; the first when sequestrated antigen(s) leaked and faced the immune system cells initiated aberrant responses [humoral ,cellular], the second case where the presence of molecular mimicking epitope on the surface of an invading viral pathogens[may be bacterial] to human subject and inducing an aberrant autoimmune responses. Autoimmune disease resulted when the virulence insult of the mimicking epitopes outweighed the immune defenses of the host. Thus ,pathogenesis can be due to; i- inflammatory damage mediated by the autoimmune overreactions ,ii-direct damage by the circulating virus reactivated on chronicity and iii-frequent continual release of the virus portions from hid. Pathological autoimmune conditions are either organ specific or generalized. Thus, human chronic viral infections may or may not be in association with autoimmunity[1,2,3]. The current circulating sars-cov-2 virus infectious pandemic disease suggested to be in association with autoimmunity[3,4] covid-19 disease may followed by long persistent consequences[3]. These consequences expresses different pathobiologic feature in different organ systems in different human subjects and varies in severity in various affected human subjects[5],. Today, nomenclature to this post- acute covid persistent cases as long- covid. Long covid as a disease entity shared many features with autoimmune disease. Autoimmunity registry ,includes long covid as an autoimmune disease[6] .In the present communication a try to review and analyze the post-infection and post-vaccination autoimmune long covid entities in comparative mechanistic approach, using a Google literature map for collection the relevant published reports.

Pathobiology of long Covid-19:

Some of the main patho-biologic features of long covid-19 have been documented ,like; Cough ,chest pain ,palpitation ,fever, dizziness ,joint pain and shortness of breath[NICE,SIGN &RCGP,2022[5],Table -1.

Table-1: An organ system wise patho-biologic features of long covid-19*.

| The affected Organ/System | Patho-biologic features |
|---------------------------|---|
| Respiratory system | Shortness of breath, cough |
| Cardiovascular system | Chest tightness ,chest pain ,palpitation |
| Nervous System | Brain fog ,headache, dizziness ,visual disturbance ,sleep disturbance |
| Gastrointestinal system | Abdominal pain, vomiting ,diarrhea, reduced appetite |
| Musculo-skeletal system | Fatigue, joint pain, muscle pain |
| Otolaryngology | Tinnitus ,Erache ,sore throat ,nasal congestion |
| Integumentary System | Skin rashes ,hair loss |

*Adapted from [5]

In accordance with the criteria proposed by Becker et al [7] from University of Cincinnati Medical Center of covid-19 syndrome sequelae, there are five categories of long covid syndrome based on the initial symptom, time of the onset, duration of the symptom and period of quiescence as type 1,2,3A,3B,4A,4B and 5. While Fernandez-de-las Penas et al.[8] considered the phase transition symptoms starting with the, undiagnosed cases and proposed a time based classification as follows :potentially infection related symptoms,4-5 weeks ,acute post covid symptom lasting more than 24 weeks. Though there some debates about these proposed classification systems[9].

Mechanistic Autoimmunity:

Normal human subjects may have baseline natural auto-reactive antibodies and auto-reactive cells. Such baseline auto-reactive entities forms the b

asis of physiological autoimmunity. The immune conversion from the baseline levels of an auto-reactive entities into clinical indicative levels constitute the bases of pathologic autoimmune state. The sorts of such pathologic autoimmunity can be single local organ or generalized in multiple organs .It may originate from genetic bases and/or environmental bases[1,2]. The mechanistic bases of autoimmune reaction are either due to sequestered antigen or molecular mimicry. The strength of an autoimmune response determine the intensity of the autoimmune tissue injuries and the severity of the resulting autoimmune conditions which either limited to local organ or involved multiple organs[10]. Basically autoimmunity may rise from two steps the loss antigen ignorance[Tolerance] and failure of regulatory T cell to control the anti-self-effector T cells[11].

Autoimmune Registry:

At Nov.9.2021.PRNewsWire/-Autoimmune Registry[6], has determined that the biomarkers of the immune system activity similar to those of many autoimmune and auto-inflammatory diseases justify the inclusion of long covid-19 on its of disease.

Google literature Map To The Autoimmune Postcovid-19 conditions:

In this paragraph tempts was made to depict the current allover the world reported post-covid-19 autoimmune conditions ;Post-infection and post- vaccination Gullian –Barre Syndrome [12,17],autoimmune haematologic disorders[21], thrombosis in pre and post covid-19 vaccination phase[22],role of sex hormone in long covid-19[23],Possible role of anti-ideotype antibodies in sars infection and vaccination[24],Gender oriented long covid-19 autoimmunity[25],latent autoimmunity correlates with humoral immune responses to sars-cov-2[26].

An Analytic Theme:

The baseline auto-reactive antibodies and cells can be found in normal human subjects as a state of physiological autoimmunity. This baseline levels may immune converted into a clinically indicative levels , when infection or vaccination insults[presence of single or multi-organ molecular mimicking epitopes] do happened to the human subjects. Such insults can lead to an autoimmune responses followed by immune tissue injuries which in turn present an autoimmune disease[25,26].

Molecular Mimicry And Long Covid-19 :

The majority of human chronic intracellular human bacterial and viral pathogens may possess shared epitopes with one or more of the human tissue cell antigens. This is known as molecular mimicry.Covid-19 has shown to be of multi-auto-reacting epitopes with the, brain ,lung, heart ,kidney and gut. Both of the sars-cov-2 infection and sars-cov2 vaccines have these potentials leading to autoimmune condition[12.17,21-25].

Post-infection Autoimmune long covid-19 :

As many as 50% of people who contract sars-cov-2 virus infection develop a syndrome known as long covid-19 ,which appear to affect a person for months ,possibly years[6].The mechanism behind post infection long covid -19 is the virus was resident in tissue hid may either shed remnants of its structural parts or reactivated a case in which continual initiation of the inflammatory and immune responses leading to a state of an aberrant immune and inflammatory conditions finally presented as an autoimmune long covid. The severity of this condition depends on extent of exposure of the immune system to the stimulant and duration of post-infection. The immune features of this disease entity are ;i-duration of the onset was 5 to 24 weeks ,ii- Tissue resident virus shed or reactivation ,iii-molecular mimicry spike protein epitope and various human tissues iv-initiation of continual auto-inflammatory and autoimmune responses ,v-expression of the disease[12,21-25] .

Post-Vaccination Autoimmune long covid-19:

Some covid-19 vaccine designs are made of mRNA containing spike protein sequence in post vaccination period and within 4-42 days. The vaccine cells will express spike protein includes spike protein specific epitope and a molecular mimicking epitope ,both initiate immune and autoimmune responses ,the former for the prevention of infection burden and the latter causes an autoimmune tissue injuries followed by disease expression. The immune features of this disease entity are ;i- the onset is 4-42 days post-vaccination ,ii-Induction by molecular mimicking epitope iii-auto-inflammatory and autoimmune response iv-autoimmune tissue injuries in continual fashion and v- An outcome of autoimmune condition[17,21-25].

A Show case Analysis of Neural Autoimmune long covid-19:

The patho-biologic features of post-infection GBS[12] is depicted in ,Table-2.And that of post-vaccination[17],Table-3.

Table 2: Patho-biologic features of post-infection neural autoimmune long covid-19 GBS[12,13,14,15,16].

| Number of patient cases | Age | Sex | Post-infection onset duration | Patho-biologic features | Diagnostic evaluation |
|---------------------------------------|--------------------|--------------------------|-------------------------------|---|--|
| 1 | 61 | female | 4 days | Acute lower extremity weakness Areflexia | CSF high protein Electrophysiology showed neurodegeneration Lymphocytopenia |
| 6 | NM* | both | 3-10 days | Lower extremity weakness Sensory defects Tetraplegia | High CRP levels Lymphocytopenia Antiganglioside antibody 3/6 Electrophysiology showed axonal demyelination |
| First series 2 Second series 2 | 39-50 48,70 | Male Male, female | | Low grade fever malase ageusia ,polyneuritis cranialis in one and diplopia in the other Extremity weakness ,parathesia ataxia, areflexia multiple cranial palsies | High CSF protein level,covid-19 positive Lymphocytopenia High CSF proteins,covid-19 negative Electrophysiology demyelinating neuropathy CSF lymphocyte 1, 6 cell/ul. |

*NM=Not mentioned

Table -3: patho-biologic features of the post-vaccine neural autoimmune long covid -19 GBS[17,18,19 ,20].

| Patient case number | Age years | Sex | Disease onset duration | Patho-biologic features | Diagnosis |
|---------------------|-----------|------|---|--|---|
| 1 | 20 | Male | 26 days post first shot Astra-vaccine | Occipital headache ,lower limb dysthezia ,diplopia | CSF mild lymphocytosis 4cell/ul,elevated protein 1,252 mg/l |
| 1 | 57 | Male | 21 day Post first Astr dose covid-vaccine | Mild back pain travel to flanks,4 days latter facial weakness, Dysathria,7 days later ,severe dysesthesia | CSF mild lymphocytosis 8 cell/ul,elevated CSF proteins2,2471 mg/l |
| 1 | 55 | Male | 29 days Post first shot astr. vaccine | Seven days prior admission ,bilateral thigh parathesia, one day later numbness developed in lumber and sacral region | CSF elevated protein 890mg/l. |
| 1 | 48 | Male | 10 days post to first shot Astra covid-19 vaccine | Motor neuron weakness left side of the face | CSF protein level 1264 mg/l. Mild lymphocytosis 8 cell/ul |

Gullian Barre Syndrome GBS has been reported in post-infection long covid-19[12,13,14,15,16] and Khan et al.[17,18,19 ,20]were reporting post –vaccination GBS .In this show case analysis a trail was tempted to analyze the case reports presented in each of which to delineate, if any ,the feature of each of which in view of the operable immune mechanisms on the bases of ;the origin of mimicking epitope , the nature of the auto-reacting effector[cells ,cells and antibodies, antibodies], the nature of the affected neural tissue ,the nature of the autoimmune tissue injury ,and the patho-biologic feature of the disease. The major immune features of the post infection-post-vaccination GBS are;

i-Inducible by molecular mimicry

ii-Cellular and humoral immune responses to peripheral and cranial nerves.

iii-Mostly involved the GBS subtypes;I,3,&4.Antiganglioside[GM1,GQ1b] antibodies may rises in these cases

iv-CSF is either acellular or with macrophages up to 25/ul and is accompanied by elevated levels of proteins

v-lympho-cytopenia and/or thrombocytopenia.

There are four immune-pathologic subtypes[17] of GBS as follows;

Subtypes I; Acute inflammatory demyelinating polyneuropathy AIDP,T cell and antibody start to attack Schwann cells and myelin epitope of the peripheral nerve roots that slow down the electro-physiologic conduction and extreme muscle weakness.

Subtype II; Acute motor sensory axonal neuropathy ,in which inflammation and degeneration of axon and motor sensory nerves immune cell interplay this pathologic changes.

Subtype III; Miller-Fisher Syndrome, besides the immune cell effector action ,the developed anti-ganglioside antibodies resulted from molecular mimicking epitopes where inducing immune system to produce antibody against microbial pathogen or against part of the vaccine cross-reacts with peripheral nerve leading to destruction of that nerve cells .Such pathology cause problem in the eye muscle, ataxia and areflexia .

Subtype IV: Acute Motor axonal neuropathy antibody and immune cells starts to attack the axon of the motor nerve and node of Ranvier the space between two Schwann cell

In an experimental GBS animal model in which antigenic preparation containing neuritogenic epitope[PNS myelin protein or peripheral nerve homogenate] was used in immune priming protocol to rat, perivascular T cell infiltrate appear around 10 to 12 days after

immunization and two to three days before myelin destruction and onset of paralysis. Lymph node cell from the immunized animal mediate the disease, the second prominent cell was monocyte which become activated by cytokine secreted from T cells. Macrophages are the main effector cells that strip myelin or cause nerve injury by reactive oxygen species ,pro-inflammatory cytokine like tumor necrosis alpha, nitric acid or production of complement .B cell ,however, contribute to the pathogenesis of GBS through CD40L-Cd40 interactions and regulatory mechanisms .B cells play a suppressive role during the induction of GBS but enhances the severity during the peak disease[27,28,29,30].

Proposal for Anti-viral-Anti-vaccine Autoimmune Long Covid-19:

In a proposal of an experimental animal settings; the auto-reactive spike protein derived from the spike protein or from recombinant protein were used for separation ,purification, .identification and quantification of the auto-reactive epitope[s] .Then the resultant epitopes will be used for immune-priming of suitable experimental animals using hyper-immunization protocols for five weeks followed by three weeks leave. Bovine ganglioside mixture using similar priming protocol as control Primed animals of the test and control animals will be checked for neurogenic abnormalities ,eviscerated and histopathology will be done for the affected nervous tissues ,to exclude or include GBS on the histo-pathologic and immunologic bases The resulted autoantibody and auto-reacting lymphocytes will be adopted for passive transfer to normal animal model to compare pathology with that of molecular mimicking epitope primed animals.[10,27,28,29,30,31].

Laboratory Biology:

Check for; CSF proteins and cellular elements ,lymphocyte and thrombocyte counts,Covi-19 genes in viral RNA by QTPCR ,anti-ganglioside and anti-motor nerve antibodies[12,17]. The is an evident overlap of post-infection and post- vaccination autoimmune long covid-19 GBS ,Table 4.

Table 4: Laboratory Biologic features of Postinfection-Postvaccination autoimmune long covid-19 GBS.[12,17,31]

| Features | Post –infection[12] | Post vaccination[17] |
|---------------------------------------|---------------------------------------|---|
| Comorbidity | +/- | +/- |
| Pathobiology | Moderate to severe progressive | Mild |
| Demyelination of PNS & cranial nerves | Mostly evident ganglioside and axonal | Demyelination not evident in the quoted cases |
| QT-PCR | Covid-19 +/- | - |
| CSF protein levels | High | High |
| Antiganglioside antibody | +/- | +/- |
| Antiaxonal antibody | +/- | +/- |

| | | |
|------------------|-----|-----|
| Lymphocytopenia | + | + |
| Thrombocytopenia | +/- | +/- |

Conclusions:

Long covid-19 has been considered as an autoimmune condition. Either single or pan-sharing molecular mimicking epitopes induces an autoimmune responses leading to local single organ/system or multiple organ immune tissue injuries terminated by either demyelination on nerve cell or axonal destructions which in turn express the pathobiology of the disease. T cell, activated macrophages and B cells as well as the auto-antibodies are involved in the immunopathogenesis of the disease. Post vaccination autoimmune long covid-19 are being difficult to be delineated from the post infection form in view of the current available knowledge and of overlapping expressions. A laboratory animal model was suggested to prove the molecular mimicry nature of the autoimmune covid-19 GBS. Post-vaccination long covid-19- GPS are being difficult to delineate from the post-infection form [except in its mild impact on peripheral nerve and absence of infection before vaccination] in view of current available knowledge and actually they were overlapping entities.

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