Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

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Abstract

A novel coronavirus, SARS-CoV-2 was identified in Wuhan, China. The disease caused by the virus can range in severity from asymptomatic to acute respiratory distress syndrome (ARDS) and death.

Primary dengue infection results in IgE mediated sensitization against dengue virus (DENV) proteins. These IgE bind to receptors on mast cells. Upon subsequent exposure to the antigen recognized by the IgE, mast cell degranulation occurs releasing mediators such as histamine. Therefore secondary dengue infection results in urticaria, increased vascular permeability, hypotension, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). A case of "slow rolling anaphylaxis".

Since vaccines contain animal proteins derived from animals infected with any number of viral diseases, one could develop IgE mediated sensitization to numerous viral proteins including coronavirus proteins. Therefore, receipt of such vaccines acts like a dengue "primary infection". It results in IgE mediated sensitization directed against coronavirus proteins. Once sensitized, a SARS-CoV-2 infection therefore now becomes the equivalent of a secondary dengue infection and similarly can have a severe course for the same reason - IgE mediated mast cell degranulation and the immune cascade that follows.

There are many common observations between COVID-19 and dengue. Elevated levels of ferritin, interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), D-dimer, coagulopathy, urticaria and ARDS are reported in both diseases.

There are many indicators that mast cell degranulation and histamine release may have a major role in COVID-19 and dengue severity. Mast cell stabilizers, antihistamines, Vitamin C, HCQ, azithromycin, ivermectin may address different aspects of this cascade and thus reduce disease severity. Disease mechanisms and immunopathology must be understood. Focusing on anti-viral action of drugs alone could be counter productive. For example, CQ had no effect on viraemia but decreased cases of DHF.

Introduction

A novel coronavirus, now named SARS-CoV-2 was identified in hospitalized patients in Wuhan, China, in December 2019. The disease caused by the virus, now named COVID-19, can range in severity from asymptomatic to acute respiratory distress syndrome (ARDS) and death.

Discussion

Primary dengue infection results in immunoglobulin E (IgE) mediated sensitization directed against dengue virus (DENV) proteins (1,2). These IgE antibodies bind to high affinity FcεRI receptors on mast cells. Upon subsequent exposure to the antigen recognized by the IgE, cross-linking of antibodies

will result in mast cell degranulation and release of mediators such as histamine. The same process occurs with IgE bound to basophils. Therefore secondary dengue infection results in such mast cell degranulation, histamine release, leading to urticaria, increased vascular permeability, hypotension, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). It can be viewed as a type 1 immediate hypersensitivity reaction with the difference that the antigen exposure is not a step function (as in say food allergy) but a ramp function as the viral replication ramps up over a few days. As a result, we have a "slow rolling anaphylaxis".

Influenza vaccines cause IgE mediated sensitization to influenza viral proteins (3–7). Upon subsequent infection with influenza virus, we have mast cell degranulation as in the case of dengue. The course of the infection is worse because we have a viral infection concurrent with an allergic reaction. As the viral load increases, so will the severity of the allergic reaction, leading to influenza shock syndrome (ISS) (8).

This concept can be generalized. Any population where a new virus/bacteria is introduced, can suffer severe disease if the population has prior IgE mediated sensitization directed against epitopes that have homology to epitopes in the novel pathogen. In nature, IgE mediated sensitization is directed against helminth/parasite antigens. However, now, for the vast majority of the world's population, helminth and parasite infections are rare. The main cause of IgE mediated sensitization is vaccines (9). Therefore, upon reports of SARS-CoV-2, protein sequence analysis was performed comparing SARS-CoV-2 proteome to the proteomes of organisms used in vaccine manufacturing. The strongest match was to a pig spike protein (from a coronavirus infected pig).
Accession number QGV12786 vs. QHD43416.1 for SARS-CoV-2. Detailed BLASTP (10) results are included in a section below. Not surprisingly, that pig spike protein also has high homology to SARS and MERS virus spike proteins.

Since vaccines contain animal proteins derived from pigs (porcine gelatin), cows (bovine serum albumin) infected with any number of viral diseases, one could develop IgE mediated sensitization to numerous viral proteins including coronavirus proteins. We have entire, viable porcine circoviruses in the rotavirus vaccines, for example (11). And of course, this is not limited to porcine material. Vaccine manufacturing derives materials from bovine, chicken and other animal sources as well. Therefore, receipt of such vaccines acts like a dengue "primary infection". It results in IgE mediated sensitization directed against coronavirus proteins. Once sensitized, a SARS-CoV-2 infection therefore now becomes the equivalent of a secondary dengue infection and similarly can have a severe course for the same reason - IgE mediated mast cell degranulation and the cascade that follows.

Rangwani (12,13) provides additional evidence on the role of mast cells in COVID-19.

Similarity between COVID-19 and dengue

There are now multiple reports from dengue endemic areas that COVID-19 is being mistakenly diagnosed as dengue (14,15). Given the reasons above, there is good reason to expect such similarity.

In COVID-19, elevated levels of ferritin (16), interleukin-6 (IL-6)(16), vascular endothelial growth factor (VEGF) (17) and D-dimer (18), have been reported. Elevated levels of ferritin (19), IL-6 (20) , VEGF (21) and D-dimer (22,21) are also reported with dengue infection. Coagulopathy is reported in both COVID-19 (18) and dengue (20). Urticaria is reported in both (14,23,24). ARDS is common in COVID-19 (25). ARDS is also described in dengue patients (26).

IgE mediated sensitization to coronavirus will result in mast cell degranulation when exposed to the SARS-CoV-2 proteins. Specifically, mast cell degranulation by cross-linking of IgE bound to high affinity FcεRI receptors on the surface of mast cells results in the release of many mediators including histamine and ferritin (27). Histamine promotes release of IL-6 (28). Elevated levels of ferritin and IL-6 are predictors for fatality in COVID-19 (16). Such IgE triggered degranulation also results in the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) (29). This results in activation of the coagulation system and elevated D-dimer levels (30). The same cascade applies to secondary dengue infection.

Such striking similarity is to be expected because of the same underlying immunological mechanisms involved in both diseases.

The parasite connection

In nature, the main role of the IgE antibody is defending against parasites. Many parasites in nature enter via the skin (malaria, hookworm). DENV is injected via the skin by a mosquito bite. Vaccines contain viral proteins derived from coronavirus infected animals. These vaccines injected through the skin, program the immune system to recognize these viral proteins (and thus the viruses) as parasites (IgE mediated sensitization). The immune system therefore inappropriately mounts an anti-parasite response against the virus upon infection, along with an anti-viral response. So it is not surprising that some anti-parasitic medications (and anti allergy medications) seem to help by suppressing the inappropriate part of the immune response.

Parasites have evolved to produce numerous decoy proteins to confuse the human immune system as an evasive measure (31). As a result, the immune system is forced to produce IgE directed against numerous proteins thus diluting the response against parasite-specific proteins. Therefore in a population where parasite infections are common, IgE mediated response to any specific protein such as viral proteins would be weak. Now, with parasite infections being rare, this protection is lost. We have strong IgE mediated responses against viral proteins, once sensitized.

Hydroxychloroquine (HCQ), chloroquine (CQ) and ivermectin (IMC) are anti-parasite medications. There are indications that they may benefit in COVID-19 (32,33) and dengue (34). There is controversy over the antiviral activity of these drugs.

Both HCQ (35) amd IMC (36) have been shown to reduce IgE levels. So it does not come as a surprise that these anti-parasite drugs have beneficial effect on viral diseases involving IgE mediated immunopathological changes. IgE is now also involved in allergies. Anti-allergy medications also can therefore help in these diseases (24).

The Dengvaxia vaccine causes simultaneous IgE mediated sensitization against all four DENV serotypes. A natural infection will cause IgE mediated sensitization directed against only one DENV serotype at a time. A secondary infection by the same serotype virus will result in severe disease. Therefore, as expected, the probability of a severe secondary infection following the Dengvaxia vaccine is much higher thus resulting in more deaths among the vaccinated. The details were previously described (37).

The exact same failure was observed in experimental SARS-CoV vaccine in mice (38). The mice developed IgE mediated sensitization to the SARS-CoV proteins following vaccination. The mice

developed "Th2-type immunopathology suggesting hypersensitivity to SARS-CoV components" when subsequently challenged with the virus.

So we have a consistent, repeating pattern of first injected exposure to SARS-CoV, dengue, influenza or coronavirus proteins resulting in IgE mediated sensitization directed against the viral proteins. Subsequent exposure to the viruses results in severe disease due to a viral infection concurrent with an allergic reaction. The first injection in the case of dengue virus can be a natural mosquito bite. In all other cases and in the case of the dengue vaccines, IgE mediated sensitization is iatrogenic and preventable.

Potential Treatments

Mast cell stabilizers work at the main source and can prevent release of histamine, elevation of ferritin, IL-6, VEGF, D-dimer levels, etc. Neutrophils recruited to the infection site release histamine (39). Antihistamines can block some of the effects of histamine.

Vitamin C has an antihistamine effect (40). Hydroxychloroquine improves IgE mediated asthma (35). Azithromycin has an anti-inflammatory effect on histamine induced inflammation (41). For these reasons, Vitamin C, hydroxychloroquine and azithromycin can help in COVID-19 (32,33).

Conclusion

COVID-19 is an iatrogenic disease caused by IgE mediated sensitization to coronavirus proteins present in vaccines containing components derived from infected animals. There are many indicators that mast cell degranulation and histamine release may have a major role in COVID-19 and dengue infection severity. Mast cell stabilizers, antihistamines, Vitamin C, HCQ, azithromycin, ivermectin may address different aspects of this cascade and thus reduce disease severity. Disease mechanisms and immunopathology must be understood. Focusing on anti-viral action of drugs alone could be counter productive. For example, CQ had no effect on viraemia but decreased cases of DHF (34).

BLASTP detailed results

QHD43416.1 surface glycoprotein [Severe acute respiratory syndrome coronavirus 2] vs. porcine spike protein (from a coronavirus infected pig)

spike protein [Sus scrofa]

Alignment statistics for match #1

Score	Expect	Method	Identities	Positives	Gaps
322 bits(824)	1e-89	Compositional matrix adjust.	234/765(31%)	361/765(47%)	101/765(13%)

```
Query  521   PATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQ   580
             P + G    ++  + C +    G  G GV+T +N  FL     + D       A ++
Sbjct  632   PKPLEGVTDVSFMTLDVCTKYTIYGFKGEGVITLTNSSFLAGVYYTSDSGQLL-AFKNVT   690

Query  581   TLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGS   640
             + + +TPCSF          S Q A + D+     V + +   + T+
Sbjct  691   SGAVYSVTPCSF------------SEQAAYVDDDI------VGVISSLSSSTFNSTRELP   732

Query  641   NVFQTRAGCLIGAEHVNNSYECDIPI----GAGICASYQTQTNSPRRARSVASQSIIAYT   696
              F         H N+   C P+     G+C S     S     S + Q  IA T
Sbjct  733   GFFY----------HSNDGSNCTEPVLVYSNIGVCKS-----GSIGYVPSQSGQVKIAPT   777

Query  697   MSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQY   756
             ++              +I+IPTNF++S+ TE L +   T  SVDC  Y+C   ++ C  LL QY
Sbjct  778   VT-----------GNISIPTNFSMSIRTEYLQLYNTPVSVDCATYVCNGNSRCKQLLTQY   826

Query  757   GSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGG--FNFSQILP----DPS   810
              + C + AL   A +     +   ++ +   I  F G  +NF+ +L      DP+
Sbjct  827   TAACKTIESALQLSARLESVEVNSMLTISEEALQLATISSFNGDGYNFTNVLGVSVYDPA   886

Query  811   KP---SKRSFIEDLLFNKVTLADAGFIKQ-YGDCLGDIAARDLICAQKFNGLTVLPPLLT   866
                    KRSFIEDLLFNKV     G + + Y C    + DL+CAQ ++G+ VLP ++
Sbjct  887   SGRVVQKRSFIEDLLFNKVVTNGLGTVDEDYKRCSNGRSVADLVCAQYYSGVMVLPGVVD   946

Query  867   DEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQ   926
             E + Y+++L+ G + G+T   AA +PF+ +  R N + +  +VL  NQ+L+A
Sbjct  947   AEKLHMYSASLVGGMVLGGFT----AAAALPFSYAVQARLNYLALQTDVLQRNQQLLAES  1002

Query  927   FNSAIGKIQDS--------------LSSTASALGKLQDVVNQNAQALNTLVKQLSSNFGA   972
             FNSAIG I +            L++ A AL K+Q+ VVN   AL  L QL  NF A
Sbjct  1003  FNSAIGNITSAFESVKEAISQTSKGLNTVAHALTKVQEVVNSQGAALTQLTVQLQHNFQA  1062

Query  973   ISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSEC  1032
             ISS ++DI SRLD + A+VQ+DRLITGRL +L  +V Q L +   E++AS  LA  K++EC
Sbjct  1063  ISSSIDDIYSRLDILSADVQVDRLITGRLSALNAFVAQTLTKYTEVQASRKLAQQKVNEC  1122

Query  1033  VLGQSKRVDFC-GKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAIC-HDGKAHFP  1090
             V QS+R  FC G G H+ S  Q+AP G++FLH   VP      +   +C +D  A
Sbjct  1123  VKSQSQRYGFCGGDGEHIFSLVQAAPQGLLFLHTVLVPGDFVDVIAIAGLCVNDEIALTL  1182

Query  1091  REGVFV--------SNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVV-IGIVNNTVYDPL  1141
             RE   V         T +FV+ R +EP+ T +     +C V + +  + + D +
Sbjct  1183  REHGLVLFTHELQNHTATEYFVSSRRMFEPRKPTVSDFVQIESCVVTYVNLTRDQLPDVI  1242

Query  1142  QPELDSFK--EELDKYFKNHTSPDVDL-----------GDISGINASVVNIQKEIDRLNE  1188
             +D K +E+     N T P + L           G+I+ +   +++   + L
Sbjct  1243  PDYIDVNKTLDEILASLPNRTGPSLPLDVFNATYLNLTGEIADLEQRSESLRNTTEELQS  1302

Query  1189  VAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIM  1233
             + N+N +L+DL+ L + E YIKWPW++WL    LI +V + +
Sbjct  1303  LIYNINNTLVDLEWLNRVETYIKWPWWVWLIIFIVLIFVVSLLVF  1347
```

While the highest homology was to the pig spike protein above, there is also strong homology to other common vaccine components such as the *Bordetella pertussis* protein below:

orf1ab polyprotein [Severe acute respiratory syndrome coronavirus 2] vs. *B. pertussis*

putative DNA helicase [Bordetella pertussis]
 [CPP87293.1](#) **394 1**

Alignment statistics for match #1

Score	Expect	Method	Identities	Positives	Gaps
55.5 bits(132)	1e-05	Composition-based stats.	89/356(25%)	140/356(39%)	61/356(17%)

```
Query  5604  LQGPPGTGKSHFA--IGLALYYPSARIVYTACSHAAVDALCEKALKYLPIDKCSRIIPAR  5661
             LQGPPG GK++    + L L    R+ ++ SH A++ L + L+ L  +   + A+
Sbjct  8     LQGPPGAGKTYTGSRVLLQLLRAGRRVAVSSNSHHAINNLL-RGLERLAEREGFALRGAK  66

Query  5662  -------------ARVE-CFDKFKVNSTLEQYVFCT--VNALP--ETTADIVVFDEISMA  5703
                          A++E  FD  V+    Q V T  + A P  E    D +  DE
Sbjct  67    KSTSAGDDSCLGGAQIEDVFDNKDVDPARHQLVAGTAWLFARPEFEQAFDYLFVDEAGQG  126

Query  5704  TNYDLSVVNARLRAKHYVYIGDPAQLPAPRTLLTKGTLEPEYFNSVCRLMKTIGPD--MF  5761
             +  +L +      A++ V +GD  QL  P       G      + +  +    TI   +F
Sbjct  127   SLANLVAMGQ--CARNIVLLGDQMQLGQPSQGTHPGRSGESALDYLLDGQATIAASQGVF  184

Query  5762  LGTCRRCPAEIVDTVSALVYDNKLKAHKDKSAQCF--------KMFYKGV----ITHDVS  5809
             L T R   EI  +S +YD +L+A   +A        ++  G+    + HD +
Sbjct  185   LDTSYRMHPEICGFISEAIYDGRLRAAPATAAHRLLLDEAAGRELPAHGIRYVPVPHDGN  244

Query  5810  SAINRPQIGVVRE---FLTRNPAWRKA-----------VFISPYNSQNAVASKIL--GLP  5853
             +  +R +  V E    L R    +A           +F++PYN Q     L  G
Sbjct  245   TQSSREEAARVAELCALLLRQRHVDEAGAPAPLTLDDILFVAPYNVQVNTLRAALPDGAR  304

Query  5854  TQTVDSSQGSEYDYVIFTQTTETAHSC-------NVNRFNVAITRAKVGILCIMS  5901
              TVD  QG E   VI + T +           + NR NVAI+RA+    + + S
Sbjct  305   VGTVDKFQGQEAQVVIVSMATSSGDYLPRDLEFLFSRNRLNVAISRARTLAILVAS  360
```

orf1ab polyprotein [Severe acute respiratory syndrome coronavirus 2] vs. *C. tetani*

ADP-ribose-binding protein [Clostridium tetani]
 [WP_023438321.1](#) **179 1**

- See 4 more title(s)

Alignment statistics for match #1

Score	Expect	Method	Identities	Positives	Gaps
41.6 bits(96)	0.077	Composition-based stats.	43/147(29%)	73/147(49%)	13/147(8%)

```
Query  1036  DNVYIKNADIVEEAKKVKPTVVVNAANVYLKHGGGVAGALNKATNNAMQVESDDYIATNG  1095
             + + I  DI +E+       +VNAAN  L  GGGV GA++KA + + E + I+  G
Sbjct  7     NKISIIKGDITKESVDA----IVNAANSVLLGGGGVDGAIHKAGGSQILKECKEIISKIG  62

Query  1096  PLKVGGSCVLSGHNL-AKHCLHVVGPNVNKGE--DIQLLKSAYENF------NQHEVLLA  1146
              L+ G + SG  L AK+ +H VGP    G    + LL + Y N         + ++
Sbjct  63    KLETGKAVITSGGKLKAKYVIHAVGPIWRGGSCNEETLLANCYINSLNLAKEKDIKTIAF  122

Query  1147  PLLSAGIFGADPIHSLRVCVDTVRTNV  1173
             P +S G++G     ++++  T++ N+
Sbjct  123   PNISTGVYGFPQDLAVKIVFKTMKENI  149
```

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