TITLE: DETECTION OF TOXIN-LIKE PEPTIDES IN PLASMA AND URINE SAMPLES FROM COVID-19 PATIENTS.

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SUMMARY

The frequent association between COVID-19 disease and different extrapulmonary clinical manifestations in symptomatic patients was reported recently.

The data reported here suggest an association between COVID-19 disease and the release in the body of (oligo-)peptides almost identical to toxic components of venoms from animals. The presence of these peptides opens new scenarios on the aetiology of the COVID-19 clinical symptoms observed up to now, including neurological manifestations.

INTRODUCTION

Numerous clinical extrapulmonary manifestations co-occuring with COVID-19 disease have been reported (as e.g. neurological, haemorrhagic, and thrombotic ones) and evidence of their severity and persistence is increasing. Gupta et al. reviewed the extrapulmonary organ-specific pathophysiology of patients with COVID-19, '*to aid clinicians and scientists in recognizing and monitoring the spectrum of manifestations, and in developing research priorities and therapeutic strategies for all organ systems involved*'[1]. Liotta et al. have characterized the incidence of neurological manifestations in a cohort of hospitalised patients with confirmed COVID-19: the most frequent were myalgia, headache, encephalopathy, dizziness, dysgeusia, and anosmia; encephalopathy was found to be '*associated with increased morbidity and mortality, independent of respiratory disease severity*'[2]. Whether these manifestations are linked to other disorders co-occurring with SARS-CoV-2 infection, is under discussion. Frontera et al., by conducting a prospective, multi-centre, observational study of hospitalised adults with laboratory-confirmed SARS-CoV-2 infection, concluded that *'neurologic disorders were detected in 13.5% of COVID-19 patients during the study timeframe. Many of these neurologic disorders occur commonly among patients with critical illness. Encephalitis, meningitis or myelitis referable to SARS-CoV-2 infection did not occur, though post-infectious Guillain-Barre syndrome was identified. Overall, neurologic disorders in the context of SARS-CoV-2 infection confer a higher risk of in-hospital mortality and reduced likelihood of discharge home'*[3].

Studies on the use of mass spectrometry in COVID-19 patients focus on the search for augmented human inflammatory molecules to be used as biomarkers to assess the severity status of COVID-19 (see for example the work of Messner et al.[4]). Our intent was to use mass spectrometry to discover the eventual presence of molecules suggested by the clinical description of neurological, coagulation and inflammatory symptoms. Therefore, our approach started from the described clinical manifestations of COVID-19 (such as hyposmia, dysgeusia, etc.).

Here we present the results of our analyses. By using mass spectrometry, we found toxin-like peptides in plasma and urine samples from COVID-19 patients, but not in control samples. As our findings do not correspond with current thinking of the aetiology related to the observed clinical manifestations in COVID-19 patients, we feel their immediate sharing with the scientific community is critical.

EXPERIMENTAL DESIGN

Samples used in the present study: plasma samples collected from 5 COVID-19 patients from different cities of Italy and from 5 control individuals (i.e. negative to SARS-CoV-2 tests and not affected by cancer or autoimmune diseases) and urine samples collected from 2 additional COVID-19 patients and from 2 control individuals.

All samples have been analysed for the presence of proteins with potential toxic effect by using the cloud ion mobility mass spectrometry (CIMS) coupled with surface activated chemical ionization-Electrospray-NIST (SANIST) Bayesian model database search (SANIST-CIMS), as described in[5,6]. The complete 'UniprotKB set of manually reviewed venom proteins and toxins'[7] (mixed with a subset of not venom proteins and toxins from UniprotKB in order to give a statistical significance to the results) was used as reference protein dataset.

Material and Methods details are in the Supplementary Materials file.

RESULTS

The presence of (oligo-)peptides characterised as toxic components of animal venoms was observed in plasma and urine samples from SARS-CoV-2 infected patients and never in plasma and urine samples from control individuals. Several (oligo-)peptides (between 70 and 115, depending on the analysed sample) matched to different animal venom proteins and toxins like conotoxins, phospholipases A2, metalloproteinases (86% of assignments have a *-log(e)* higher than 25).

A list of 36 proteins covered by the toxin-like peptides found is reported in Table 1. A selection of representative spectra for 30 of them is reported in Supplementary Materials (Figure S1).

Some of the toxin-like peptides found mapped on the same reference protein (UniprotKB:D2DGD8), are reported in Figure 1: these peptides were found in the five plasma samples. Interestingly, looking at the characteristics of toxin-like peptides mapped on proteins known to be secreted and matured, in some cases we noticed that the functional C-terminal region was abundant in plasma samples, the signal peptide and propeptide (N-terminal) were more abundant in urine samples (data not shown, in preparation).

DISCUSSION

The types of toxic-like peptides found resemble known conotoxins, phospholipases A2, metalloproteinases, prothrombin activators, coagulation factors, usually present in animal venoms, which are known to have high specificity and affinity towards human ion channels, receptors and transporters of the nervous system, like the nicotinic acetylcholine receptor.

What follows is our attempt to understand a potential relation between their presence and extrapulmonary COVID-19 symptomatology.

Conotoxins.

Conotoxins are a group of neurotoxic peptides isolated from the venom of the marine cone snail of the genus *Conus*. Mature conotoxins consist of 10 to 30 amino acid residues and typically have one or more disulfide bonds. These

disulfide patterns are used to define the structural classes of conotoxins (μ-conotoxins, ω-conotoxins, and α-conotoxins are the major classes). They are soluble in water and have a variety of mechanisms of actions, most of which have not yet been determined[8]. However, it has been shown that many of these peptides modulate the activity of several receptors, including ion channels, nicotinic acetylcholine receptors (nAChRs) and enzymes (acetilcholinesterases) that degrade acetylcholine, thus resulting in the alteration of acetylcholine levels and of cholinergic transmission[9,10,11].
The presence of conotoxin-like peptides might explain the occurrence of many symptoms (like hyposmia, hypogeusia and the signs typical of Guillain-Barre syndrome) observed in some COVID-19 patients. Their presence can alter normal functioning of ion channels, nicotinic acetylcholine receptors and of acetylcholine levels.

Phospholipases A2.
Phospholipases A2 (PLA_2, E.C. 3.1.1.4) hydrolyse phospholipids and lead to release of lysophosphatidic acid and arachidonic acid[12]. Arachidonic acid is a major precursor of many pro-inflammatory mediators like leukotreines, thromboxanes and prostaglandins; as a consequence, abnormal presence of active PLA_2 can induce severe inflammation[13]. In animal venoms, PLA_2 act as neurotoxic proteins that bind to and hydrolyse membrane phospholipids of the motor nerve terminal (and, in most cases, the plasma membrane of skeletal muscle) to cause a severe inflammatory degenerative response that leads to degeneration of the nerve terminal and skeletal muscle[12]. The drug dexamethasone is able to inhibit the prostaglandins synthesis and leukotriene formation[14]. As dexamethasone is still the only therapeutic shown to be effective against the novel coronavirus in patients[15] with severe symptoms, it can be that the positive effect of this drug on COVID-19 patients is also due to the reduction of the here identified PLA_2-like peptides.

Metalloproteinases.
The last example of identified toxin-like peptides is about those recognised as metalloproteinases present in animal venoms, zinc-dependent enzymes of varying molecular weights having multidomain organization. These toxic enzymes cause haemorrhage, local myonecrosis, skin damage, and inflammatory reaction[16]. It has been reported that symptomatic COVID-19 patients have significantly lower zinc levels in comparison to controls and that zinc deficient patients develop more complications[17]. The presence of this specific group of toxin-like peptides, which capture zinc, can be one of the reasons for such significantly low zinc levels in symptomatic COVID-19 patients.

Similarity searches by TBLASTN[18] with relaxed parameters at the National Center for Biotechnology Information (NCBI) website (see Materials and Methods) revealed (in addition to mRNA sequences from the animal species reported in Table 1) almost identical short stretches (up to 10 amino acids) of these peptides in potential coding regions of many bacterial and viral sequences, but no long potential coding frame entirely covering any of them was found. Consequently, at the time of writing we have not yet identified the "genetic source" of these peptides, which could be:

- The SARS-CoV-2 RNA genome with its protein reading set, as proposed by Brogna[19], who reported the identification in SARS-CoV-2 RNA of many regions encoding for oligopeptides (four - five amino acids long) identical to neurotoxin peptides typical of animal venoms.
- The SARS-CoV-2 genome directly read by bacteria, assuming that SARS-CoV-2 genome, or parts thereof, is capable of replicating with a possible 'bacteriophage-like' mode of action, as previously described in [20].
- Genomes of bacteria, which, as a reaction to the presence of the virus, secrete these peptides. This could be achieved by using still not well known and controversial mechanisms, like alternative reading due to rRNA sequence heterogeneity (as described in[21-22]), or the involvement of small bacterial ncRNA (sRNAs), known to be important regulators of gene expression under specific conditions (like stress response, quorum sensing, and virulence; Coleman at al., in 1984 described the first evidence of a functional sRNA of bacterial origin with the characterization of *micF* non-coding RNA[23]).
- A combination of the above: e.g. the 'toxin' genetic code is present in the bacteria and expression may be triggered by SARS-CoV-2, acting like temperate bacteriophages, which are known to interact with bacteria so that they express (or not) certain genes, as described by Carey et al.[24].

A detailed 3D structural similarity analysis between the toxin-like peptides found and reference proteins has not yet been conducted. Accordingly, at the time of writing, we can only speculate that these toxin-like peptides are involved in the clinical extrapulmonary manifestations in symptomatic COVID-19 patients. In addition, according to our knowledge, these toxin-like peptides have never been searched in animals considered reservoirs of SARS-CoVs.

The results reported here raise questions additional to those already listed by us in [20]:

- Are these finding in line with what proposed by Tizabi et al. [24], i.e. a potential therapeutic role for nicotine, nicotinic agonists, or positive allosteric modulators of nicotinic cholinergic receptors in COVID-19?
- If induced by SARS-CoV-2, can the production of toxin-like peptides be involved in the neurological disorders and injuries observed in hospitalized COVID-19 patients?
- If induced by SARS-CoV-2, can the production of toxin-like peptides influence complex diseases apparently triggered or enhanced by COVID-19, like e.g. Guillain-Barré Syndrome[25] or Parkinson's disease[26] ?
- Are toxin-like peptides associated to SARS-CoV-2 infection or to other viral infections or, more in general, is their presence related to sickness condition?
- Are our findings supporting the suggestion made by the iVAMP Consortium[27] on the relationships between animal venom glands and microorganisms' microenvironments?

We consider that the immediate sharing of these results can contribute to the untangling of the multifaceted set of clinical manifestations in symptomatic COVID-19 patients, and to the further understanding of the mechanisms involved.

DECLARATIONS

The scientific output expressed does not imply a policy position of the European Commission. Neither the European Commission nor any person acting on behalf of the Commission is responsible for the use that might be made of this publication.

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The here reported proteins have been deposited as pending patent for the development of antitoxins and antibodies (ITA 102020000023809) by Craniomed Group srl.

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FIGURES AND TABLES LEGENDS

Figure 1. Alignment of the toxin-like peptides to Conotoxin Pu6.1.
Conotoxin Pu6.1 from *Conus pulicarius* (UniprotKB:D2DGD8) is aligned with the toxin-like peptides identified in four out of five plasma samples. Being the protein secreted and cleaved, leader-region pro-peptide and mature cysteine rich domains are highlighted in green, yellow and red, respectively. Each identified toxin-like peptide is named according to the sample of origin and its uniqueness. For each of them, the number reported in square brackets indicates the number of identical toxin-like peptides identified in the same sample.

Table 1. Overview of proteins on which toxin-like peptides have been mapped.
36 candidate protein sequences on which the identified toxin-like peptides have been mapped are here reported, together with information retrieved from UniprotKB and Taxonomy databases. The table is split in 3 sections, according to the phylum of the reported species: Chordata (green), *Echinodermata* (pink), *Mollusca* (azure).

Figure S1. Examples of spectra
31 spectra are reported, as representative set of 30 toxin-like peptides mapped on the proteins reported in Table 1.

TABLE 1

UNIPROTKB CANDIDATE'S INFORMATION							TAXONOMY CANDIDATE'S INFORMATION			
AC	*ID*	*Status*	*Protein name*	*ENZYME EC*	*Other name(s)*	*Length (aa)*	*ID*	*Species*	*Phylum - Family*	*Organism's common name(s)*
Q8AY46	VKTHB_BUNCA	reviewed	Kunitz-type serine protease inhibitor homolog beta-bungarotoxin B1 chain	NA	-	85	92438	*Bungarus candidus*	***Chordata*** - *Elapidae*	. Malayan krait
A6MEY4	PA2B_BUNFA	reviewed	Basic **phospholipase A2** BFPA	EC 3.1.1.4	. Antimicrobial phospholipase A2 . Phosphatidylcholine 2-acylhydrolase (svPLA2)	145	8613	*Bungarus fasciatus*	***Chordata*** - *Elapidae*	. Banded krait . Pseudoboa fasciata
F5CPF1	PA235_MICAT	reviewed	**Phospholipase** A2 MALT0035C	EC 3.1.1.4	. Phospholipase A2 MALT0035C (svPLA2)	142	129457	*Micrurus altirostris*	***Chordata*** - *Elapidae*	. Uruguayan coral snake . Elaps altirostris
A8QL59	VM3_NAJAT	reviewed	Zinc **metalloproteinase**-disintegrin-like NaMP	EC 3.4.24.-	. Snake venom metalloproteinase (SVMP)	621	8656	*Naja atra*	***Chordata*** - *Elapidae*	. Chinese cobra
Q9I900	PA2AD_NAJSP	reviewed	Acidic **phospholipase A2** D	EC 3.1.1.4	. svPLA2 . APLA . Phosphatidylcholine 2-acylhydrolase	146	33626	*Naja sputatrix*	***Chordata*** - *Elapidae*	. Malayan spitting cobra . Naja naja sputatrix
Q58L90	FA5V_OXYMI	reviewed	Venom **prothrombin activator** omicarin-C non-catalytic subunit	NA	. vPA . Venom coagulation factor Va-like protein *Cleaved into 2 chains*	1460	111177	*Oxyuranus microlepidotus*	***Chordata*** - *Elapidae*	. Inland taipan . Diemenia microlepidota
Q58L91	FA5V_OXYSU	reviewed	Venom **prothrombin activator** oscutarin-C non-catalytic subunit	NA	. vPA . Venom coagulation factor Va-like protein *Cleaved into 2 chains*	1459	8668	*Oxyuranus scutellatus*	***Chordata*** - *Elapidae*	. Coastal taipan
Q9W7J9	3S34_PSETE	reviewed	Short **neurotoxin** 4	NA	. SNTX4 . Alpha-neurotoxin 4	79	8673	*Pseudonaja textili*	***Chordata*** - *Elapidae*	. Eastern brown snake
P23028	PA2AD_PSETE	reviewed	Acidic **phospholipase A2** homolog textilotoxin D chain	NA	. svPLA2 homolog	152	8673	*Pseudonaja textilis*	***Chordata*** - *Elapidae*	. Eastern brown snake
Q593B6	FA5_PSETE	reviewed	**Coagulation factor** V	NA	*Cleaved into 2 chains*	1459	8673	*Pseudonaja textilis*	***Chordata*** - *Elapidae*	. Eastern brown snake
Q7SZN0	FA5V_PSETE	reviewed	Venom **prothrombin activator** pseutarin-C non-catalytic subunit	NA	. PCNS . vPA . Venom coagulation factor Va-like protein *Cleaved into 2 chains*	1460	8673	*Pseudonaja textilis*	***Chordata*** - *Elapidae*	. Eastern brown snake
Q2XXQ3	CRVP1_PSEPL	reviewed	Cysteine-rich venom protein ENH1	NA	. CRVP . Cysteine-rich secretory protein ENH1 (CRISP-ENH1)	239	338839	*Pseudoferania polylepis*	***Chordata*** - *Homalopsidae*	. Macleay's water snake . Enhydris polylepis
Q9PW56	BNP2_BOTJA	reviewed	**Bradykinin**-potentiating and C-type natriuretic peptides	NA	. Brain BPP-CNP . Evasin-CNP *Cleaved into the 12 chains*	265	8724	*Bothrops jararaca*	***Chordata*** - *Viperidae*	. Jararaca
A8YPR6	SVMI_ECHOC	reviewed	Snake venom **metalloprotease** inhibitor	NA	. 02D01 . 02E11 . 10F07 . Svmpi-Eoc7 *Cleaved into 15 chains*	308	99586	*Echis ocellatus*	***Chordata*** - *Viperidae*	. Ocellated saw-scaled viper
Q698K8	VM2L4_GLOBR	reviewed	Zinc **metalloproteinase**/disintegrin [Fragment]	EC 3.4.24.-	*Cleaved into 3 chains*	319	259325	*Gloydius brevicaudus*	***Chordata*** - *Viperidae*	. Korean slamosa snake . Agkistrodon halys brevicaudus
Q8AWI5	VM3HA_GLOHA	reviewed	Zinc **metalloproteinase**-disintegrin-like halysase	EC 3.4.24.-	. Zinc metalloproteinase-disintegrin-like halysase . Snake venom metalloproteinase (SVMP) . Vascular apoptosis-inducing protein (VAP)	610	8714	*Gloydius halys*	***Chordata*** - *Viperidae*	. Chinese water mocassin . Agkistrodon halys
P82662	3L26_OPHHA	reviewed	Alpha-**neurotoxin**	NA	. Alpha-elapitoxin-Oh2b (Alpha-EPTX-Oh2b) . Alpha-elapitoxin-Oh2b . LNTX3 . Long neurotoxin OH-6A/OH-6B . OH-3	91	8665	*Ophiophagus hannah*	***Chordata*** - *Viperidae*	. King cobra . Naja hannah
Q2PG83	PA2A_PROEL	reviewed	Acidic **phospholipase A2** PePLA2	EC 3.1.1.4	. Phosphatidylcholine 2-acylhydrolase (svPLA2)	138	88086	*Protobothrops elegans*	***Chordata*** - *Viperidae*	. Elegant pitviper . Trimeresurus elegans
P06860	PA2BX_PROFL	reviewed	Basic **phospholipase A2** PL-X	EC 3.1.1.4	. Phosphatidylcholine 2-acylhydrolase (svPLA2)	122	88087	*Protobothrops flavoviridis*	***Chordata*** - *Viperidae*	. Habu . Trimeresurus flavoviridis
P0C7P5	BNP_PROFL	reviewed	**Bradykinin**-potentiating and C-type natriuretic peptides	NA	. BPP-CNP *Cleaved into 6 chains*	193	88087	*Protobothrops flavoviridis*	***Chordata*** - *Viperidae*	. Habu . Trimeresurus flavoviridis
Q3C2C2	PA21_ACAPL	reviewed	**Phospholipase A2** AP-PLA2-I	EC 3.1.1.4	. Phosphatidylcholine 2-acylhydrolase (svPLA2)	159	133434	*Acanthaster planci*	***Echinodermata*** - *Acanthasteridae*	. Crown-of-thorns starfish
D6C4M3	CU96_CONCL	reviewed	**Conotoxin** Cl9.6	NA	. Conotoxin Cl9.6	81	1736779	*Californiconus californicus*	***Mollusca*** - *Conidae*	. California cone . Conus californicus
D2Y488	VKT1A_CONCL	reviewed	Kunitz-type serine protease inhibitor **conotoxin** Cal9.1a	NA	-	78	1736779	*Californiconus californicus*	***Mollusca*** - *Conidae*	. California cone . Conus californicus
D6C4J8	CUE9_CONCL	reviewed	**Conotoxin** Cl14.9	NA	-	78	1736779	*Californiconus californicus*	***Mollusca*** - *Conidae*	. California cone . Conus californicus
P0DPT2	CA1B_CONCT	reviewed	Alpha-**conotoxin** CIB [Fragment]	NA	. C1.2	41	101291	*Conus catus*	***Mollusca*** - *Conidae*	. Cat cone
V5V893	CQG3_CONFL	reviewed	**Conotoxin** Fla16d	NA	. Conotoxin Fla16d *Cleaved into 2 chains*	76	101302	*Conus flavidus*	***Mollusca*** - *Conidae*	. Yellow Pacific cone
P58924	CS8A_CONGE	reviewed	Sigma-**conotoxin** GVIIIA	NA	. Sigma-conotoxin GVIIIA	88	6491	*Conus geographus*	***Mollusca*** - *Conidae*	. Geography cone . Nubecula geographus
P0DM19	NF2_CONMR	reviewed	**Conotoxin** Mr15.2	NA	. Conotoxin Mr15.2 (Mr094)	92	42752	*Conus marmoreus*	***Mollusca*** - *Conidae*	. Marble cone
P0C1N5	M3G_CONMR	reviewed	**Conotoxin** mr3g	NA	. Conotoxin mr3g (Mr3.6)	68	42752	*Conus marmoreus*	***Mollusca*** - *Conidae*	. Marble cone
D2DGD8	I361_CONPL	reviewed	**Conotoxin** Pu6.1	NA	-	83	93154	*Conus pulicarius*	***Mollusca*** - *Conidae*	. Flea-bite cone
P0C8U9	CA15_CONPL	reviewed	Alpha-**conotoxin**-like Pu1.5	NA	-	81	93154	*Conus pulicarius*	***Mollusca*** - *Conidae*	. Flea-bite cone
A1X8B8	CA1_CONQU	reviewed	Putative alpha-**conotoxin** Qc alphaL-1	NA	. QcaL-1	68	101313	*Conus quercinus*	***Mollusca*** - *Conidae*	. Oak cone
P58786	COW_CONRA	reviewed	**Contryphan**-R	NA	. Bromocontryphan *Cleaved into 2chains*	63	61198	*Conus radiatus*	***Mollusca*** - *Conidae*	. Rayed cone
P58811	CA1A_CONTU	reviewed	Rho-**conotoxin** TIA	NA	. Rho-TIA	58	6495	*Conus tulipa*	***Mollusca*** - *Conidae*	. Fish-hunting cone snail . Tulip cone
Q5K0C5	O16A_CONVR	reviewed	**Conotoxin** 10	NA	-	79	89427	*Conus virgo*	***Mollusca*** - *Conidae*	. Virgin cone
B3FIA5	CVFA_CONVR	reviewed	**Conotoxin** Vi15a	NA	. Conotoxin Vi15.1	74	8765	*Conus virgo*	***Mollusca*** - *Conidae*	. Virgin cone

FIGURE 1

D2DGD8 - I361_CONPL Conotoxin Pu6.1 (*Conus pulicarius*)