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Neurological Implications and Mental Health of COVID-19

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Abstract
Background and Objectives: Its well known that the COVID-19 is disease causes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), less known that the COVID-19 can attach the brain through the olfactory nerve in the nasal cavity and damage neurons that control breathing of central nervous system (CNS). The aim of this study is to understand the multiple adverse impact of the COVID-19 on mental and neurological health, to urge the physicians and healthcare staff to apply psychological first aid regarding the anxiety and stress as well as to attract specific attention to the neurological implications.
Methods: A literature research was carried out through PubMed and Psyc INFO between 1990 and 2020. One hundred and fifteen articles were recruited. A first part of this review describes the COVID-19 crisis and consequences. The second part focuses on research about the interrelation between COVID-19, mental and neurological diseases.
Results: It reveals that the Psychological and behavioural states and CNS processes are associated with immune functions and there is a relationship between stress, anxiety and the immune system. Long-term anxiety and panic attacks based on the COVID-19 pandemic can cause the brain to release stress hormones on a regular basis which weakness the immune system. It also reveals that third of the COVID-19 Chinese patients had damage in the nervous system which cause a severe acute respiratory syndrome.
Conclusion: Anxiety and stress (AS) can be serious symptom of the COVID-19 pandemic. AS can cause the brain to release stress hormones that weakness the immune system which in turn infect the body with the COVID-19. The corona virus can go into the brain trans-neuronally through the olfactory pathways to cause serious complication. Hence, the respiratory syndrome can occur due to brainstem involvement. Thus, brain imaging and pathological evaluation of the brain are necessary to understand the full impact of the COVID-19.

Keywords: COVID-19, Virus, pandemic, olfactory, brain, neurology, psychology

Introduction

Coronavirus disease 2019 (COVID-19) is a disease which attacks not only the respiratory system but It can also attack the central nervous system (CNS). Its, since the early beginning of 2020, well known that COVID-19 is a disease causes a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Figurs1).

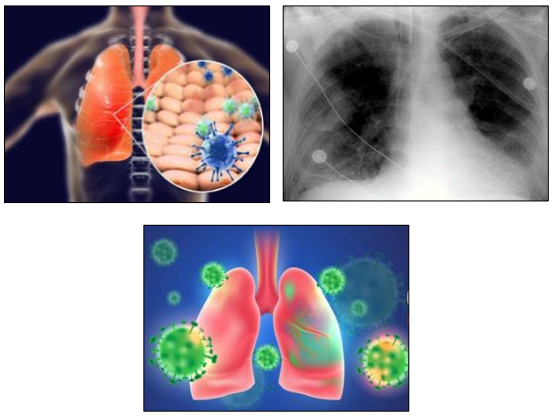

Fig 1: Covid-19: Corona viruses-lung-china-pathogen respiratory-influenza

Less known is that the COVID-19 may enter the brain through the olfactory nerve in the nasal cavity and damage neurons that control breathing of the CNS (figures 2).

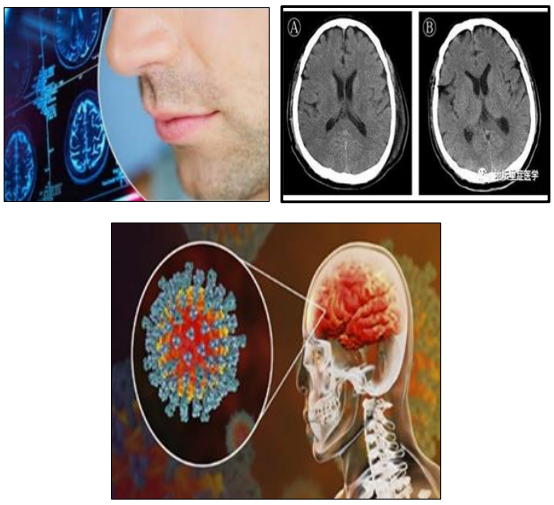

Fig 2: COVID-19 attack the Olfactory impacting the brain

According the John Hopkins University Covid-19 dashboard, which collates information from national and international health authorities, the outbreak of the novel virus "COVID -19" since 31 December 2019 has left more than 1 777 666 infected people with significant outbreaks in the US, Italy, Spain and France and UK. The total number of deaths is 108, 867. As shown in Table 1, these 5 countries are the most affected by the pandemic with approx. 75% of the deaths [1].

Table 1: The 10 countries most affected by COVID-19 worldwide (122 of 197) & some other random countries.

		Total confirmed	Total Deaths	Total recovered	Case fatality ratio	Deaths/per 100.000
	Worldwide7,8 billion	**1 777 666**	**108,867**	**404,372**	**6.1%**	
1.	US	526,396	20,463	32 001	3.9%	6.25
2.	Italy	152,271	19,468	32,534	12.8%	32.22
3.	Spain	163,027	16,606	59,109	10.2%	35.54
4.	France	130,727	13,851	26,671	10.6%	20.68
5.	United Kingdom	79,874	9,892	625	12.4%	14.88
6.	Iran	70,029	4,357	41,947	6.2%	5.33
7.	Belgium	28,018	3,346	5, 986	11.9%	29.29
8.	China	83,014	3,343	77,877	4.0%	0.24
9.	Germany	124,908	2,736	57,400	2.2%	3.30
10.	Netherlands	24,571	2,653	291	10.8%	15.40
-	-	-	-		-	-
14.	Sweden	10,151	887	381	8.7%	8.71
24.	Denmark	6,191	260	2,111	4.2%	4.48
33.	Norway	6,409	119	32	1.9%	2.24
30.	Egypt	1,939	146	426	7,5	0.15
35.	Russia	13,584	106	1,045	0.8%	0.07
36.	Israel	10,743	101	1,341	0.9%	1.14
47.	Ukraine	2,511	73	79	2.9%	0.16
53.	Finland	2,905	49	300	1.7%	0.89
59.	Moldova	1,560	30	75	1.9%	0.85
68	Belarus	2,226	23	172	1.0%	0.24
72.	Lebanon	619	20	77	3.2%	0.29
121.	Latvia	630	3	16	0.5%	0.16
122.	Zimbabwe	14	3	-	21.4%	0.02

However, the sudden chock put most nations and people in a panic, anxiety and fear state even with the medical sciences and advanced technology. Unprepared nations almost failed to address the mental health and neurological aspects amongst the population because all efforts are focused on understanding the epidemiology, clinical features with focus on pneumonia and other respiratory symptoms and treatments [2].

The COVID-19 itself reveals that the entire healthcare system in majority of worldwide countries could potentially be overwhelmed and could crumble. Signs of that are already evident in New York also many of the grocery stores are with empty shelves, pharmacies are running out of critical medications and there is scarcity of personal protection equipment and ventilators [3].

Objectives and method

The aim of this study is to shed light on the multiple adverse impact on mental and neurological health, to be able to implement adequate steps to tackle and provide a background to physicians and healthcare workers at the time of such outbreaks to apply psychological first aid regarding the anxiety, stress and possible depression as well as to attract specific attention to the Neurological Implications. A theoretical literature and other sources review have are offering a systematic analysis of the main research framework, lines and empiric evidences available about COVID-19 pandemic crisis in subjects with psychology and neurology. With this purpose, a literature research was carried out through PubMed and PsycINFO between 1990 and 2020. The descriptors used were "COVID-19", "coronavirus 2", "SARS-CoV-2", "pandemic and psychological diseases" pandemic and neurological diseases". One hundred and fifteen articles were recruited, including theoretical, quasi-experimental, and descriptive studies. Studies that included COVID-19 young patients were excluded because of exceeding the scope and main goals of this review. Findings were grouped into two thematic blocks. The first part of this review describes the COVID-19 crisis and consequences and the second part focuses on research about the interrelation between COVID-19, mental and neurological diseases.

COVID-19 and the psychological diseases

The outbreak of coronavirus disease 2019 (COVID-19) is often stressful unhealthy phenomena. Fear and anxiety about the corona infection disease are now quite overwhelming and cause strong emotions in both adults and children.

Stress during COVID-19 disease outbreak can include anxiety, fear and worry about own health and the health of other family members, relatives and friends; changes in sleep and insomnia; dating disorder; concentrating difficulty, worsening of chronic health problems, worsening of mental health conditions and weakening of the immune system. In panic disorder as a result of the VOVID-19 pandemic, a role of central CRH in panic attacks use to appear. Atrial natriuretic peptide (ANP) is causally involved in sodium lactate-induced panic attacks [4].

The anxiety and stress responses, the hypothalamic pituitary adrenocortical (HPA) system and its modulation by corticotropin-

releasing hormones (CRH), corticosteroids,and their receptors, and the roles of natriuretic peptides and neuroactive steroids should be analyzed. We review the role of the HPA system in major depression, panic disorder, and post-traumatic stress disorder and its possible relevance for treatment. Impaired glucocorticoid receptor function in major depression is associated with an excessive release of neurohormones such as CRH, to which a number of signs and symptoms characteristic of depression can be ascribed. Post-traumatic anxiety and stress disorder can be characterized by a peripheral hyporesponsive (HPA) system and elevated CRH concentrations in the CSF.[5] The COVID-19, can thus increase risk of disorder. Normalization of HPA system abnormalities is a strong predictor of the clinical course, at least in major depression and panic disorder which maybe generate by the COVID-19.

The Psychological and behavioral states and CNS processes are associated with immune function. Many previous studies indicates that there is a relationship between anxiety and the immune system. Stress and immunity have comprehensively been investigated but relatively few studies of anxiety and immunity. Many of the neurobiological processes associated with stress and with depression have been observed in anxiety and are known to influence the immune system.

The biologic effects of stress on immunity are multifaceted, including complex neuroendocrine and neurotransmitter interactions. It appears that the psychological responses to the COVID-19 which generate a lot of anxiety and life stress need to be considered in the investigation of behavior, and immunity [6].

COVID-19 and Neurological implications

COVID-19 causes too much Anxiety and Stress (AS). Anxiety has a intricate relation and correlation with the immune system. Too much anxiety can be a serious reason to threaten weaken the immune system dramatically. Anxiety generate stress which release the stress hormone “cortisol”. Although, anxiety does not cause sickness, it weaken the immune system when there is contact with germs. There is a complex correlation between the post-traumatic stress which is requiring more prospective research in order to determine causal relationships between thesepathologies.7 The body needs a strong immune system keep the body safe from bacteria, viruses and germs. It struggle to fight the viruses and germs back. Every time a human ingest a virus, a germ or a bacteria, the body's healthy and strong immune system destroys it quickly. The immune system actually is trained to fight and to do whatever it takes to keep the body form getting sick.

A recent study showed that nervous system manifestations is significantly more common in severe infections compared with nonsevere infections. They included acute cerebrovascular disease such as ischemic stroke and cerebral hemorrhage and respiratory failure, impaired consciousness and skeletal muscle injury. However, according to Mao *et al*. (2020) [8], there are three Neurologic manifestations categories:

1. Central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure),
2. Peripheral nervous system (PNS) manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and
3. Skeletal muscular injury manifestations. Impaired consciousness includes the change of consciousness level (somnolence, stupor, and coma) and consciousness content (confusion and delirium).

However, We are still in the dark because there have been very few examinations of the brain of COVID-19 patients. But, a very recent report from Wuhan is published in 2020 in the journal "JAMA Neurology", found that third of 214 examined patients showed signs that the COVID-19 virus had damaged the nervous system (Mao *et al*, 2020) [8]. Figure 3 shows the brain and the chest images as a result of a serious COVID-19 symptoms.

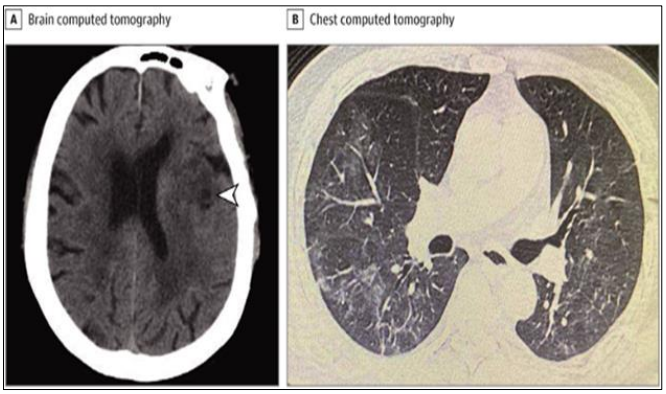

Fig 3: The COVID_19 infected brain and chest images

The most common symptoms of the brain damage included dizziness and headache, as well as olfactory and taste disorders.

a. Brain CT image 1 day after ischemic stroke. White arrowhead indicates the ischemic lesion.
b. Chest CT image 1 day after ischemic stroke.

Its an evidence that the COVID-19 patients can lose their sense of smell and taste, at least temporarily. These symptoms indicated that the brain was involved as shown in Figure 3.

Anosmia requires the involvement of the olfactory bulbs. In mouse models of coronavirus encephalitis, the virus could enter the brain trans-neuronally through the olfactory pathways [9] to damage the respiratory syndrome. The major neurobiological processes associated with stress have also been observed in depression [6]. Thus, focus and consideration of the effect of stress on the immune system may provide further understanding of the biology of depressive disorders which maybe caused by COVID-19. Stress-induced modulation of immunity is complex and involves a range of neurobiological mechanisms.

In panic disorder as a result of the VOVID-19 pandemic, a role of central CRH in panic attacks use to appear. Atrial natriuretic peptide (ANP) is causally involved in sodium lactate-induced panic attacks.

The anxiety and stress responses, the hypothalamic pituitary adrenocortical (HPA) system and its modulation by corticotrophin-releasing hormones (CRH), corticosteroids, and their receptors, and the roles of natriuretic peptides and neuroactive steroids should be analyzed. We review the role of the HPA system in major depression, panic disorder, and post-traumatic stress disorder and its possible relevance for treatment. Impaired glucocorticoid receptor function in major depression is associated with an excessive release of neuro hormones such as

CRH, to which a number of signs and symptoms characteristic of depression can be ascribed [5]. Depression and aggression are also comorbid symptoms of stress and anxiety [10].

Post-traumatic anxiety and stress disorder can be characterized by a peripheral hypo-responsive HPA system and elevated CRH concentrations in the CSF. The COVID-19, can thus increase risk of disorder. Normalization of HPA system abnormalities is a strong predictor of the clinical course, at least in major depression and panic disorder which maybe generate by the COVID-19.

Long-term anxiety and panic attacks based on the COVID-19 pandemic can cause the brain to release stress hormones on a regular basis which in turn increase the frequency of symptoms such as headaches, dizziness, and depression and weakness the immune system and its mechanism. (Figure 4)

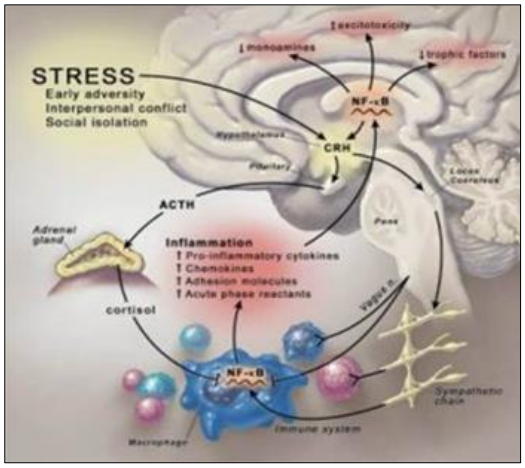

Fig 4: Anxiety, Stress hormones and immune system.

Anxiety can have a significant negative effect on the body, and long-term anxiety as a result of the COVID-19 increases the risk of developing chronic physical conditions. Different medical research suspects that anxiety develops in the amygdala which is an area of the brain that manages emotional responses. Many physical symptoms are correlated with different diagnosis of all anxiety disorders, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [3].

Anxiety and stress can contribute to high blood pressure, heart disease, obesity diabetes, chest pain, headaches, insomnia, heart palpitations and skin rashes. Stress can cause anxiety and anxiety is a reaction to the stress. CS stress and anxiety disorders are strongly associated with a substantial loss of life quality [1, 2].

When people feel anxious and stressed, the brain floods to the nervous system with hormones and chemicals such as adrenaline and cortisol designed to help to respond to a COVID-19 threat.

Cortisol prevents the release of substances that cause inflammation, and it turns off aspects of the immune system that fight infections, impairing the body's natural immune response. As a result of the threats of the COVID-19, people with panic and anxiety disorders may be more likely to get the COVID-19 infection. Thus, there is an urgent need for new prevention strategies.

Conclusion

A considerable number of the neurobiological processes are associated with anxiety, stress and depression have been observed and are known to negatively influence the immune system. The biologic effects of stress on immunity are multifaceted, including complex neuroendocrine and neurotransmitter interactions. As a result of the outbreak of the COVID-19, people with panic and anxiety disorders may be more likely to be infected by the COVID-19. Thus, there is an urgent need for new prevention tools and strategies. Long-term anxiety and panic attacks based on the COVID-19 pandemic can cause the brain to release stress hormones on a regular basis which in turn increase the frequency of symptoms such as headaches, dizziness, and depression and weakness the immune system and its mechanism.

Finally, some recent examinations of the brain of COVID-19 patients shows that third of the infected COVID-19 patients had damage in the nervous system. The most common symptoms of the brain damage included dizziness and headache, as well as olfactory and taste disorders which cause a severe acute respiratory syndrome. Thus, brain imaging and pathological evaluation of the brain are necessary to understand the full impact of the COVID-19.

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