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COVID-19 and developmental origins of health and disease

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ABSTRACT

From the moment of the identification of SARS-CoV-2 as an etiological agent of the severe clinical pictures of pneumonia that were being slowly observed all over the world, numerous studies have been conducted to increase the knowledge about what was an unknown virus until then. The efforts were mainly aimed to acquire epidemiological, microbiological, pathogenetic, clinical, diagnostic, therapeutic and preventive information in order to increase the available weapons to fight an infection which was rapidly taking on the characteristics of the pandemic. Given the topicality of the problem, not everything has yet been fully understood and clarified, especially in the maternal-fetal-neonatal field, where we are beginning to question what could be the outcomes of newborn babies born to mothers who contracted SARS-CoV-2 infection during pregnancy. Thus, the aim of this review is to analyze the long-term outcomes of this infection that could affect the offspring, regardless of a possible maternal-fetal transmission, focusing on, above all, the role of maternal immune activation and the expression of the Angiotensin-converting enzyme 2 (ACE2) in particular at the placental level.

1. Introduction

At the end of 2019 in Wuhan, in the Hubei province in China, they identified a new specie of Coronavirus that was responsible for a growing number of cases of fever associated with breathing difficulties [1]. This virus was then called SARS-CoV-2, and the pathology caused by it, COVID-19 (Corona-Virus Disease-2019) [2].

Over the months, in parallel with the spread of the infection all over the world, there has been a progressive increase in knowledge related to this pathology and its causative agent, but many aspects remain to be clarified, especially in the maternal-fetal-neonatal context. In particular, the debate on the possibility of a vertical transmission of the virus is still open: in fact, although most of the studies published so far show that this occurrence is unlikely [3–6], a recent case report [7] would have documented its transplacental transmission and other papers have discussed the cases of vertical transmission [8,9].

On the contrary, it is well known that maternal infections contracted during pregnancy [10,11], or pathologies of the pregnant woman with an immune component (such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes mellitus, asthma, hypothyroidism) [10] or conditions associated with a pro-inflammatory status such as a high BMI [11] or

social stress [11], lead to a so-called Maternal Immune Activation (MIA) which in the long term could be responsible for the onset of psychiatric disorders in the offspring, with schizophrenia and autism spectrum disorders (ASD) above all [12].

Furthermore, given the strong tropism of SARS-CoV-2 for the respiratory system, the maternal hypoxia that could follow the infection would represent a noxa able to disrupt the fetal and perinatal environment, thus causing an alteration of the fetal programming mainly regarding the expression of Angiotensin-converting enzyme 2 (ACE2) and the components of the associated pathway at the level of various fetal organs as well as at the placental level [13,14]. This alteration would form a molecular basis for the onset, not only in adulthood, but also in childhood and adolescence, of metabolic and cardiovascular pathologies [13].

Thus, the aim of this review is to analyze the long-term outcomes of this infection that could affect the offspring, regardless of a possible maternal-fetal transmission, focusing on, above all, the role of maternal immune activation and the expression of the ACE2 in particular at the placental level.

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2. The role of Maternal Immune Activation (MIA)

The fetal brain development process is an elaborate and delicate event. Any external influence could potentially be able to compromise it, causing permanent structural and functional alterations with severe consequences for the unborn child [15].

Among the factors capable of interfering with the proper execution of this process there are maternal infections contracted during pregnancy [16]. These can act in this direction through two main mechanisms: with pathogenic-specific effects (as shown for example by the correlation between microcephaly and infection in pregnancy with the Zika virus) [17] or by triggering the maternal immune response towards the infectious agent itself [15]. In particular, the finding of the activation of similar cytokine pathways, as well as an increased risk for offspring to develop the same disorders, despite the fact that different pathogens were responsible for the maternal infection from time to time, made us lean towards the immune response or the maternal immune activation (MIA) against them, as a common mechanism at the basis of neuropsychiatric pathologies that can be found in the offspring in the long term [15]. To confirm this, some authors began to study the effects of MIA on animals using a synthetic preparation as a trigger for the maternal immune response. This preparation is called "Poly (I:C)" or polyinosinic-polycytidyl acid, a synthetic analogue of a double helix RNA molecule (dsRNA) [15].

The latter is commonly found during the replication cycle of several viruses [15], therefore the Poly (I:C) is able to mimic perfectly a viral infection [18]. Indeed, its administration is able to cause a maternal immune response mediated by Toll-Like-Receptor 3 (TLR3), exactly like that caused by the agents that are most often responsible for infections in pregnancy (CMV, influenza virus, rubella virus) [15].

It is also important to consider the expression of TLR3: at placental level it represents one of the most expressed TLR [19], thus placing itself in a strategic position between the infectious/inflammatory maternal event and the effects on fetal development.

The mediators would be several proinflammatory cytokines. Indeed, a study by Chudnovets et al. [20] highlights the role of IL-1 β in the genesis of adverse neurological sequelae in offspring.

In particular, through an increase in the levels of NF- κ B and caspase-1 at the level of the placenta and of the fetal brain, it would determine in these districts, in a dose-dependent manner, structural and functional changes, with consequent reduction of fetal vitality, dysfunction and neuronal damage, behavioral changes in survivors, with cerebral palsy, autism spectrum disorders (ASD) and schizophrenia as main long-term consequences. Furthermore, the authors highlight that the probability that persistent rather than temporary brain anomalies will occur during fetal life depends on the concentration and timing of exposure to IL-1 β , thus making this a potential therapeutic target to be blocked in order to prevent the genesis of future neuropsychiatric pathologies of the offspring.

Another factor capable of influencing the neurological outcome would be the degree of basal immunoreactivity (BIR) of a woman before pregnancy: intermediate levels of BIR, in particular, would be more harmful than high levels [21]. According to the authors, this could be due to the context and the intrinsic properties of maternal cytokines which are proinflammatory at intermediate levels, while the same cytokines are anti-inflammatory at high levels, thus high levels of BIR may be protective [21].

The same consequences (ASD, schizophrenia, cerebral palsy) are also described by Yockey et al. [22]. According to them, however, there would be an increase in maternal blood levels, not of IL-1 β , but of IL-17, as an effect of MIA. It would be able to act on fetal cortical neurons resulting in an increased activity of the neurons of the somatosensitive cortex which in turn would correlate with the aforementioned behavioral alterations. Furthermore, in the case of viral infection in pregnancy, an immune response could also be triggered at the placental and fetal level which, like MIA, could contribute to the dysregulation of fetal

development processes, probably through an increase in the levels of IL-1 β , IFN- γ and TNF- α , whose role in detail has not yet been clarified [23,24].

According to Choi et al. [25], actually, the serum levels of IL-17A (member of the IL-17 family) would increase late, i.e. only 48 h after the induction of MIA through the administration of the poly (I:C) in the animal model. Instead, it would be IL-6 to play a role in the very early stages of the maternal inflammation: it is considered to be necessary and sufficient for the induction of ASD in the offspring [26].

Even Rasmussen et al. [11] underline the role of IL-6, which would be a key mediator as a sensor, transducer and effector of external influences on fetal brain development [27].

In particular, an increase in its concentration in maternal blood as an expression of MIA, in any trimester of pregnancy, would cause an alteration at the level of the frontolimbic circuitry, a critical structure for both cognitive and socio-emotional development [11]. Therefore, this would correlate with the onset in the offspring of pathologies with symptoms that refer to psychiatric spheres, such as ASD, but also schizophrenia, anxiety disorder, psychopathy and conduct disorder [11].

The systemic inflammatory state caused by IL-6 in the pregnant woman would also be exacerbated in case of gestational diabetes mellitus (GDM) [28]. This, like MIA, is in itself capable of increasing the risk for offspring to develop ASD [29] or schizophrenia [30]. In addition, the resulting hyper-glycaemia and hyperinsulinemia can in turn prolong the body's responsiveness to pro-inflammatory stimuli [31,32]. Thus, GDM and MIA would be able to empower each other and the association of the two events would therefore create a maternal inflammatory state not only more intense but also mediated by different pathways than those activated by each of them. These pathways are involved also in the differentiation of dopaminergic neurons and in the innate immune response, as well as in the genesis of the aforementioned neuropsychiatric disorders [28].

The correlation between MIA and altered immune response in offspring has also been proposed by Valtanen et al. [33]. Indeed, according to the authors, maternal inflammation would interfere not only with the development of the fetal nervous system but also with that of its immune system. By investigating the role played by the different proinflammatory cytokines in the onset of various neuropsychiatric disorders associated with MIA, a study [34] describes how this correlates with an increased risk of ASD in the offspring through an alteration of the expression of genes involved in the pathophysiology of this type of disorders.

In addition to schizophrenia and ASD, MIA may also be associated with an increased risk of developing bipolar disorder and ADHD [10,35]. With regard to the latter, a study [36] would relate it to maternal fever during pregnancy, in fact this would cause hyper-thermic damage to the fetal neurons.

More specifically, the authors of this study would have observed a significant association between fever and ADHD only in a specific period of gestation, i.e. in case of fever between the 9th and 12th week of pregnancy, while taking into consideration all three trimesters, the same association would not be confirmed [35].

On the other hand, according to Chudal et al. [10], a potential cause of ADHD in childhood could be an exaggerated inflammation of the fetal CNS in response to a pre or perinatal insult [36], such as a severe viral respiratory infection, as supported by a Colombian study [35]. By the analysis of the maternal C-reactive protein (CRP) values in the first trimester and at the beginning of the second, however, it was found that high values do not correlate with the development of ADHD in the offspring [37], similarly to what was observed for bipolar disorder and contrary to what was seen instead for ASD and schizophrenia [10]. This is an evidence of how different pathways are involved in the link between MIA and different neuropsychiatric disorders, and how the development of one rather than the other is actually the result of a complex interaction of the individual external perturbations and/or

among themselves (as observed for example in the case of the GDM + MIA association) and with the maternal, fetal, or genetic background [28].

Furthermore, a high maternal PCR before the 20th week of gestation was correlated with an increased risk of preterm birth and of being born small for gestational age (SGA) [38]. It is a condition that in turn would expose the offspring to increased mortality and perinatal morbidity [39] as well as to develop, in the long term, not only behavioral and neuro-evolutionary disorders [40] but also cardiovascular and metabolic diseases, with a higher incidence of hypertension, hyperlipidemia, insulin and leptin -resistance, metabolic syndrome, central adiposity and type 2 diabetes mellitus [41,42].

From these latest works, therefore, it emerges that the timing of fetal exposure to maternal inflammation is also able to influence the outcomes of the offspring. Indeed, according to a recent study [43], a strong MIA during the first trimester of pregnancy would then be associated with a greater expression, in both genders, of externalizing symptoms such as, for example, aggressiveness and impulsiveness; vice versa in the second trimester it would correlate with internalizing symptoms such as social withdrawal, sadness and uneasiness, but only in females. Thus, it seems that fetal sex can interfere with the onset of certain neuropsychiatric disorders rather than others as well. Ultimately, the occurrence of such externalizing or internalizing symptoms would then be associated with an increased risk of developing schizophrenia, depression and substance use disorder [43].

The different proposed mechanisms to explain how MIA is able to affect the fetal development and subsequently lead to different pathologies in the offspring mainly of neuropsychiatric nature are summarized in Table 1.

3. The role of ACE2

ACE2, in addition to representing the receptor through which SARS-CoV-2 penetrates the host cells, is one of the components of the Renin-Angiotensin System (RAS). In this system, it counteracts the vasoconstrictor, proliferative, angiogenic, proinflammatory and pro-fibrotic effects of Angiotensin II (AngII) by determining its conversion into

Table 1
Relationship between maternal immune activation (MIA) and offspring diseases.

Event	Involved cytokines	Proposed mechanism	Long-term outcomes
MIA	IL-1 β , NF-kB, Caspase-1 [20]	Structural and functional changes of the placenta and fetal brain [20]	ASD, schizophrenia, cerebral palsy [20]
	IL-17 [22]	Increased activity of the neurons of the somatosensitive cortex [22]	ASD, schizophrenia, cerebral palsy [20]
	IL-6, IL-17A [25]	IL-6 (early) [25]	ASD [25]
	IL-6 [11]	IL-17A (late) [25]	
		Frontolimbic circuitry alteration [11]	ASD, schizophrenia, anxiety, conduct disorder, psychopathy [11]
	IL-6 [28]	Exacerbation of maternal systemic inflammatory status in the case of GDM, and vice versa [28]	ASD, schizophrenia [28]
	IL-6	Interference with fetal immune development [33]	Altered immune response [33]
	IL-6	Alteration of the expression of genes involved in the pathophysiology of ASD [34]	ASD [34]
	IL-6	Maternal fever with hyperthermic damage of fetal neurons [35]	ADHD [35]
	IL-6	Fetal CNS inflammation [10]	ADHD [10]

MIA: maternal immune activation, ASD: Autism Spectrum Disorder, GDM: Gestational Diabetes Mellitus, CNS: Central Nervous System.

Angiotensin 1–7 (Ang (1–7)), a heptapeptide responsible - following the interaction with its own receptor (MasR) - of diametrically opposite effects [13,44,45]. In addition to this main pathway, Ang (1–7) can also be produced directly from Angiotensin I by a metal endopeptidase called Nephililase (NEP), or by ACE and NEP starting from Angiotensin 1–9, which in turn derives from Angiotensin I following the cleavage operated by ACE2 [45].

Normally, during a pregnancy all the components of the RAS intervene so that it runs physiologically.

In particular, during the early stages of gestation it is possible to observe high circulating levels of the elements of the ACE-AngII-AT1R axis (AT1R = Angiotensin II-Type1-Receptor), in order to promote decidualization, trophoblastic proliferation and therefore the embryo implantation [46,47]. While, during the intermediate and late phases, there is an increase not only in plasmatic but also in placental levels of ACE2 and, consequently, in Ang (1–7), which underlies an increase in placental blood flow and allows the rapid growth of the fetus [48,49].

Although there are conflicting opinions [50], the presence of the enzyme ACE2 has been demonstrated at the level of the maternal-fetal interface and also at the level of some fetal organs, such as the heart, lungs and liver [51]. On the basis of all this, we can thus draw two considerations: on one hand, there would be, at least from a molecular point of view, the basis for a vertical transmission of the SARS-CoV-2; on the other hand, the aforementioned role played by ACE2 in regulating placental blood flow and, consequently, fetal growth, opens up important scenarios regarding the impact of a possible dysregulation of the ACE2-Ang (1–7)-MasR axis on the longterm well-being of the offspring. This dysregulation can be secondary to several events, which in turn can be related more or less directly to the SARS-CoV-2 infection during pregnancy. Indeed, the maternal hypoxia that could follow the infection, as well as the stress condition that this could constitute, would result in noxae capable of perturbing the fetal and perinatal environment and consequently causing an alteration of fetal programming, mainly concerning the expression of the different components of the RAS at the level of the placenta and some fetal organs [13,14]. Specifically, there would be an accentuation of the expression of the ACE-AngII-AT1R axis and a long-term attenuation of that of the ACE2-Ang (1–7)-MasR axis, which in turn would affect vessels, fetal kidneys and brain with a subsequent impairment of autonomic functions and blood pressure regulation mechanisms. All this will eventually predispose the offspring to develop not only in adulthood, but also in childhood and adolescence, hypertension and, thus, cardiovascular diseases [13]. Furthermore, the impact of the alteration of fetal programming described above would seem to be greater in teenage girls rather than in boys, and in particular in those who are overweight or obese. This remarks what has already been said about MIA and the role of fetal gender in affecting the long-term outcomes of the offspring, and adding, in addition, the role of the BMI [13,52].

At the placental level, however, maternal hypoxia causes a reduction in the levels of mRNA coding for ACE2 with consequent alteration of the local vascularization. This, due to the loss of the vasodilating action of Ang (1–7), will result in a decrease in the fetal-placental blood flow and therefore, in a reduced supply of nutrients to the fetus with consequent reduction of its growth causing Intra-Uterine Growth Restriction (IUGR) [14,53].

The same vascular alterations, and thus the same impaired fetal growth, could also be due to the administration of glucocorticoids during the third trimester of pregnancy [43] to favor the lung maturation of the fetus in anticipation of a preterm birth, a not-rare occurrence, for example, in case of maternal SARS-CoV-2 infection [54]. This administration, in addition to causing a reduction in the ACE2 and Ang (1–7) placental levels, is also associated with an increased expression of the latter receptor (MasR) and of NEP, probably for a compensation mechanism [45].

Preterm birth itself, in turn, calls into question the ACE2 among the various mechanisms underlying the development of Bronchopulmonary

dysplasia (BPD) [55]. In this case, the ventilatory support given to the premature infant can lead to a so-called Ventilator-Induced Lung Injury (VILI), with consequent lung inflammation. Furthermore, a subsequent possible condition of hyperoxia would correlate with the onset of a fibrosis, an alteration which, together with the aforementioned inflammatory framework, is typically found in BPD [55,56]. In particular, the link between hyperoxia and pulmonary fibrosis is represented by a down-regulation of the ACE2 at the level of fetal lung fibroblasts [57]. The ACE-2 in fact, physiologically, is simultaneously able to induce apoptosis of the lung fibroblasts through Ang (1–7) and MasR and to inhibit the pathway activated by the AngII. Indeed, the activation of this AngII pathway leads to the transcription of inflammatory factors and pro-fibrotic cytokines as well as the conferment of resistance to apoptotic processes to pulmonary fibroblasts [58]. Thus, it can be understood how the down-regulation of the ACE2-Ang (1–7) -MasR axis, operated for example by hyperoxia, has the effect of losing the protective mechanisms against the onset of pulmonary fibrosis and therefore correlates with the development of BPD [55–58].

A further study supporting the correlation between ACE2 and offspring pathologies is for example that of Yamaleyeva et al. [59]. In this study, knockout mice for the gene encoding the enzyme ACE2, showed, during pregnancy, endothelial dysfunction affecting the uterine artery with increased reactivity to vasoconstrictor agents, placental hypoxia and reduced velocity of umbilical blood flow, resulting in the development of IUGR.

Genetic variations such as single nucleotide polymorphisms (SNP) of the ACE2 gene would also be associated with an increased risk of SGA [42]. These conditions, as we have seen, would therefore seem to represent the main consequences of an alteration of the ACE2 axis. Furthermore, as it has been discussed in the paragraph relating to MIA as well, in turn they would expose the progeny to an increased mortality and perinatal morbidity [39] and to develop, in the long term, behavioral and neuroevolutionary disorders [40] and/or cardiovascular and metabolic diseases, with a higher incidence of hypertension, hyperlipidemia, insulin- and leptin-resistance, metabolic syndrome, central adiposity and type 2 diabetes mellitus [41,42].

The pathological conditions in whose genesis the alteration of the ACE2-Ang (1–7)-MasR axis would play an important role are summarized in Table 2.

4. Discussion

In literature, it is well known that infections during pregnancy are eventually harmful for the fetus and SARS-CoV-2 seems to be no exception. The main general theory is that MIA together with the virus or the bacteria can damage the fetuses and their long-term brain development.

But the reality is really more complex than that.

Evidence from both animal studies and from the experiences in the neonatal ward show that sometimes pregnancies are resilient from infections with no damage for the fetuses.

A key role in both the resilience and the eventual damages to the

fetus is exerted by the placenta.

The placenta is not an innocent bystander but it is considered to be the black box of pregnancy. It records and it is affected by any event that may occur during pregnancy [60]. Moreover, there is a direct link between the placenta and the brain, the so-called placenta-brain axis. In addition, the placenta is the source of neurotransmitters during the fetal neurodevelopment [61]. While it is set to protect the pregnancy, in case of adverse events, such as a viral infection, like COVID-19, its defensive mechanisms could not be sufficient to prevent the harmful effects of the virus. Furthermore, in these cases, the placenta could produce damaging molecules that would negatively affect the development of the fetus. Indeed, evidence from an animal study showed that after a hypoxic event, the placenta could produce molecules that can damage both the anatomy and the function of the neurons [62].

While, for what concerns the maternal immune activation (MIA), some investigators found that high levels of MIA may actually be protective for the offspring [21]. This could be due to the fact that high levels of maternal immune mediators, especially cytokines, may act as anti-inflammatory molecules and prevent the detrimental effects on the brain [21].

In humans we have very few information concerning the vertical transmission of SARS-CoV-2 and its effect during pregnancy [63]. This type of transmission, according to very recent studies seems to be very probable with preterm labor and fetal distress as main consequences. While neonates born from SARS-CoV-2 positive mothers can experience neurological symptoms, breathing problems and pneumonia [7,8,9,21]. Furthermore, the SARS-CoV-2 was found in the amniotic fluid, in the placenta and in the cord blood of infected women. These discoveries could give a biological plausibility of the risk of intrauterine infection for the fetuses [64].

But not everything is lost [65].

A very recent study published on Cell, made a breaking discovery concerning breastmilk.

First, it confirms the hypotheses, which is already been discussed in many studies, that this virus is not found in breastmilk of infected mothers. But very little is known about the protective effect of breastmilk against COVID 19. These authors demonstrated that at 4–6 weeks after the infection, the breastmilk of these mothers contains SARS-CoV-2 spike protein antibodies (Ig A), secretory antibodies binding to the Receptor Binding Domain (RBG) and/or IgG and IgM binding RBD [66].

These Igs-A against SARS-CoV-2 are secreted because the lactating mammary gland is a part of the secretory immune system. In general, the antibodies produced by these glands are very specific and targeted to a given infectious agent. Thus, breastfeeding can be considered an ingenious immunologic integration of mother and child [67,68].

In addition, breast milk contains its own microbiota, called MOM, which protects the baby, stimulates the proper development of the immune system and colonizes its guts [69]. The good bacteria of the microbiota, such as *Lactobacilli* spp. must be protected in order to prevent infections of babies. Indeed, investigators are suggesting to be careful with the administration of antibiotics early in life [70].

Another very important component of human breast milk are the

Table 2
Relationship between ACE2-Ang (1–7) -MasR axis and offspring diseases.

Event	Ras alteration	Consequences	Long-term outcomes
Maternal hypoxia and stress [13]	↑fetal ACE-AngII-AT ₁ R axis [13] ↓fetal ACE2-Ang(1–7)-MasR axis [13]	Blood pressure and autonomic functions dysregulation [13]	Hypertension and cardiovascular diseases [13]
Maternal hypoxia [14]	↓placental ACE2 (mRNA) [14]	Alteration of the placental vascularization → IUGR [14]	Hypertension, hyperlipidaemia, insulin and leptin resistance, metabolic syndrome, central adiposity, T2DM [41,42]
Glucocorticoid administration [45]	↓placental ACE2 and Ang(1-7) [43] ↑ placental MasR and NEP [45]	↓blood flow and placental and fetal growth → IUGR [45]	
Preterm delivery, hyperoxia [55–58]	↓ACE2-Ang(1–7)-MasR axis at the level of fetal lung fibroblasts [55–58]	Loss of protective mechanisms against pulmonary fibrosis [55–58]	BPD [55–58]

T2DM: type 2 diabetes mellitus; BPD: bronchopulmonary dysplasia; IUGR: IntraUterine Growth Restriction.

stem cells. These stem cells are able to migrate into the newborn's body, cross the blood brain barriers and become neurons [71].

Further studies are needed involving the different “omics” sciences of human breast milk in order to understand the therapeutic potential of this magical fluid [72].

5. Conclusions

The SARS-CoV-2, similarly to SARS-CoV and MERS-CoV, would not seem to be transmitted vertically from the mother to the fetus [54], and the recent case report [7] stating the opposite would require further studies to refute this thesis.

These assertions, however, in the light of the knowledge acquired on maternal immune activation (MIA) and on the pathophysiological role of ACE2 at the fetal-placental level, must not make us fall into the error of thinking that infants born to mothers who have contracted COVID-19 during pregnancy are definitively safe from any impact of this infection on their health.

On the other hand, given the huge amount of data that are being produced one should not be alarmed. This new disease must be analyzed in a balanced way. The best thing to do for these infants born to COVID-19 positive mothers is to keep them monitored even during the intra-uterine life and in the long term, in order to give them the most adequate and personalized healthcare.

CRedit authorship contribution statement

Stefano Forestieri: Conceptualization, Methodology, Investigation, Writing - Original Draft.

Roberta Pintus: Writing - Original Draft.

Maria Antonietta Marcialis: Investigation, Writing - Review and Editing.

Maria Cristina Pintus: Investigation, Writing - Review and Editing.

Vassilios Fanos: Conceptualization, Supervision.

Declaration of competing interest

None declared.

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