REVIEW

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Cerebral hypoperfusion in autism spectrum disorder

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Cerebral hypoperfusion, or insufficient blood flow in the brain, occurs in many areas of the brain in patients diagnosed with autism spectrum disorder (ASD). Hypoperfusion was demonstrated in the brains of individuals with ASD when compared to normal healthy control brains either using positron emission tomography (PET) or single-photon emission computed tomography (SPECT). The affected areas include, but are not limited to the: prefrontal, frontal, temporal, occipital, and parietal cortices; thalami; basal ganglia; cingulate cortex; caudate nucleus; the limbic system including the hippocampal area; putamen; substantia nigra; cerebellum; and associative cortices. Moreover, correlations between symptom scores and hypoperfusion in the brains of individuals diagnosed with an ASD were found indicating that the greater the autism symptom pathology, the more significant the cerebral hypoperfusion or vascular pathology in the brain. Evidence suggests that brain inflammation and vascular inflammation may explain a part of the hypoperfusion. There is also evidence of a lack of normal compensatory increase in blood flow when the subjects are challenged with a task. Some studies propose treatments that can address the hypoperfusion found among individuals diagnosed with an ASD, bringing symptom relief to some extent. This review will explore the evidence that indicates cerebral hypoperfusion in ASD, as well as the possible etiological aspects, complications, and treatments.

Key words: autism, cerebral hypoperfusion, regional cerebral blood flow, positron emission tomography, PET imaging, single-photon emission computed tomography, SPECT imaging

INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental syndrome that begins before three years of age and is characterized by pervasive deficits in social interaction, impairment in verbal and nonverbal communication, and stereotyped patterns of interests and activities (American Psychiatric Association 2013). Although there is no consensus on the cause of ASD, it is considered to involve multiple environmental and genetic risk factors (Al-Ayadhi and Camel 2013, Saad et al. 2016). The interplay between genetic and environmental factors has become the subject of intensified research in the last several years (Coleman and Gilberg 2011, Deth et al. 2008).

Even though ASD is mainly diagnosed based on behavioral criteria which identify alterations in social interaction, deficits in verbal and nonverbal receptive/expressive behaviour and speech, typically including hyper-focused repetitive behaviors (Raymond et al. 2014), there is some evidence indicating that ASD is a medical disease involving multiple organs (Baumann 2010, Bjørklund 2013, Geier et al. 2012, Kern et al. 2014,

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Li et al. 2014). Some examples of health or medically related issues that appear to be a consistent part of the pathological picture in ASD include cerebral hypoperfusion, oxidative stress, neuroinflammation, gastrointestinal inflammation and dysbiosis, immune dysregulation, mitochondrial dysfunction, and neurotransmitter abnormalities (El-Ansary and Al-Ayadhi 2012, Essa et al. 2002). Moreover, many of these findings were correlated with core symptoms of ASD (Kern et al. 2012).

In this review of the scientific literature up to date, the focus will be on cerebral hypoperfusion, or insufficient blood flow in the brain, in patients with ASD. Evidence that indicates cerebral hypoperfusion in ASD will be discussed, as well as the possible etiological aspects, complications, and treatments.

Evidence for cerebral hypoperfusion

Cerebral hypoperfusion has been demonstrated in ASD as compared to healthy controls in many parts of the brain, typically using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) (Boddaert and Zilbovicius 2002, Galuska et al. 2002, Sasaki 2015, Zilbovicius et al. 1995, 2000). Further scanning methods such as fMRI were also adopted in ASD neuro-imaging with encouraging results (Dichter 2012, Jann et al. 2015, Philip et al. 2012). The hypoperfusion was detected on an individual basis in nearly 75% of the ASD children, with the current sensitivity of the imaging method (Zilbovicius et al. 2000). Furthermore, it has also been suggested that perfusion worsens with age in children diagnosed with ASD (Wilcox et al. 2002); however, this latter finding is not consistent (Zilbovicius et al. 1995).

Studies using SPECT to examine perfusion in ASD

Most of the studies indicating cerebral hypoperfusion in ASD are conducted using SPECT. Some examples of studies that have found hypoperfusion in ASD using SPECT are as follows: Starkstein et al. (2000) compared 30 patients diagnosed with ASD (11.1±7.0 years of age) and 14 patients (11.2±4.3 years of age) diagnosed with mental retardation, but no ASD, finding that patients diagnosed with ASD have significantly lower cerebral blood perfusion than the mentally retarded group in the right temporal lobe (basal and inferior areas), occipital lobes, thalami, and left basal ganglia (Starkstein et al. 2000).

Wilcox et al. (2002) examined blood flow using SPECT in 14 individuals diagnosed with ASD and 14 controls, ranging in age from 3 to 37 years and found significant hypoperfusion in the prefrontal areas of individuals diagnosed with ASD as compared to controls. Sasaki et al. (2010) examined children, 4–16 years of age, diagnosed with both ASD and epilepsy. In all of the children, results showed a mixed hypoperfusion pattern, especially involving the prefrontal cortex, medial frontal cortex, anterior cingulate cortex, medial parietal cortex, and/or anterior temporal cortex.

Gupta and Ratnam (2009) assessed the cerebral perfusion in ten children diagnosed with ASD and mental retardation, 4–8 years of age, and found generalized hypoperfusion in all ten cases as compared to age-matched controls. Frontal and prefrontal regions revealed maximum hypoperfusion. Subcortical areas also indicated hypoperfusion. Ito et al. (2005) examined regional cerebral blood flow (rCBF) pattern in individuals diagnosed with high-functioning ASD (9–14 years of age) and found significant hypoperfusion in the left temporal region compared to controls (7–15 years of age).

Degirmenci et al. (2008) found that when comparing ten children diagnosed with ASD (6.9±1.7 years) with five age-matched nonautistic children, statistically significant hypoperfusion was found in the children diagnosed with an ASD in the right inferior and superior frontal, left superior frontal, right parietal, right mesial temporal and right caudate nucleus (Degirmenci et al. 2008). More recently, Yang et al. (2011) examined 23 children (7.2±3.0 years of age) diagnosed with an ASD and 8 age-matched controls and found significant reduction in rCBF bilaterally in the frontal lobe (frontal poles, arcula frontal gyrus) and bilaterally in basal ganglia in the ASD group, and in the Asperger syndrome group a decrease in the bilateral frontal, temporal, parietal lobes and also in cerebellum, compared to the perfusion in control children. Interestingly, in the less affected children with Asperger syndrome, they found a pronounced asymmetry in the hemispheric hypoperfusion.

Also, using SPECT, Kaya et al. (2002) examined rCBF in 18 individuals diagnosed with ASD (mean age: 6.13±1.99 years) and 11 nonautistic controls (mean age: 6.5±3.39 years) to determine the relationship between rCBF and the scores of the Ritvo-Freeman Real Life Rating Scale, intelligence quotient (IQ) levels, and age. Hypoperfusion in rCBF in children diagnosed with ASD, compared with the control group, was found in bilateral frontal, frontotemporal, temporal, and temporo-occipital regions. However, they found no relationship between rCBF and the Ritvo-Freeman Real Life Rating Scale. Burroni et al. (2008) examined rCBF in 11 children diagnosed with an ASD (mean age 11.2 years) and eight age-matched controls. There was a global reduction of cerebral blood flow (CBF) in the

children diagnosed with ASD when compared with the control group, and also a significant difference for the right-to-left asymmetry of hemispheric perfusion between the two groups, with a right-sided CBF-reduction prevalence greater in children diagnosed with an ASD, as compared to the controls.

Mountz et al. (1995) studied rCBF in six individuals (mean age 13.7 years of age, ranging from 9 to 21 years of age) in reportedly severely affected individuals diagnosed with ASD and age-matched controls. The rCBF was abnormally low predominately in the temporal and parietal lobes, with the left cerebral hemisphere showing greater rCBF abnormalities than the right.

Ryu et al. (1999) studied 23 children aged 28–92 months diagnosed with ASD, and they were found to have decreased perfusion in the cerebellar hemisphere, thalami, basal ganglia, and posterior parietal and temporal areas. Interestingly, even though the children had extensive perfusion impairments, the children's magnetic resonance imaging results were considered normal (Ryu et al. 1999).

George et al. (1992) scanned four young adults diagnosed with ASD and four age-matched controls. They stated that SPECT revealed not only a regional decrease in perfusion in ASD predominately in the right lateral temporal and right, left, and midfrontal lobes compared with controls, but also a decreased global perfusion ranging from 58% to 72% of controls.

Studies using PET to examine perfusion in ASD

PET, to a lesser extent than SPECT, has also been used to examine hypoperfusion in ASD. Examples of studies that have found hypoperfusion in individuals diagnosed with an ASD using PET are as follows: Zilbovicius et al. (1995) examined rCBF in five children diagnosed with ASD at the age of 3–4 years and again three years later. They found frontal hypoperfusion in the children diagnosed with ASD at ages 3–4 years, but then three years later it had normalized by 6–7 years of age. Later, Zilbovicius et al. (2000) measured rCBF in 21 children diagnosed with ASD (8–13 years of age) and in ten nonautistic children with idiopathic mental retardation and found highly significant hypoperfusion in both temporal lobes centered in associative auditory and adjacent multimodal cortex in the children diagnosed with ASD. Brunelle et al. (2009) examined 77 children diagnosed with ASD and found reduced blood flow in the superior temporal sulcus of 21 of the children diagnosed with ASD along with the loss of grey matter. When these children were presented with sounds, there was no activation in the superior temporal sulcus, contrary to normal children, signifying disruption in complex sensory inputs in the areas of hypoperfusion.

Pagani et al. (2012) also using PET examined rCBF at rest in 13 adults diagnosed with ASD with normal intelligence (20–48 years of age) compared to ten IQ-, sex- and age-matched healthy controls (20–42 years of age). The adults diagnosed with ASD showed significant CBF increases in the right para-hippocampal, posterior cingulate, primarily visual and temporal cortex, putamen, caudatus, substantia nigra and cerebellum as compared to controls (Pagani et al. 2012). However, no correlation between CBF and IQ was found. The limbic, posterior associative and cerebellar cortices showed increased blood flow in ASD.

Cerebral hypoperfusion associated with symptomatology in ASD

Studies indicate that not only rCBF is consistently decreased in ASD, but cerebral hypoperfusion is also related to symptomatology. Using SPECT on 23 children diagnosed with ASD with a mean age of 6.5 years (SD=2.4, range 2.6–13) and 26 non-autistic age- and gender-matched controls, Ohnishi et al. (2000) reported a correlation between syndrome scores and rCBF. Each syndrome was associated with a particular pattern of perfusion in the limbic system and the medial prefrontal cortex. They stated that the perfusion abnormalities seemed to be related to the cognitive dysfunction observed in ASD, such as abnormal responses to sensory stimuli, and the obsessive desire for sameness. The perfusion patterns suggest possible locations of abnormalities of brain function underlying abnormal behavior patterns in ASD individuals (Ohnishi et al. 2000).

In another study using SPECT, mentioned earlier, Starkstein et al. (2000) found that decreased blood flow to the thalamus in patients diagnosed with an ASD was associated with repetitive, self-stimulatory, unusual behaviors, a negative attitude towards changes in routine and environment, and unusual sensory interests.

Furthermore, decreased IQ in individuals diagnosed with ASD has been associated with hypoperfusion of the temporal and frontal lobes (Hashimoto et al. 2000). Difficulties in processing facial expressions and emotions were correlated with a decreased blood flow to the temporal lobes and amygdala (Critchley et al. 2000). Difficulties in recognizing familiar faces were correlated with a decreased blood flow to the fusiform gyrus (Pierce et al. 2004), and decreased blood flow to the Wernicke's and Brodmann's areas was correlated to impairments in language development and auditory processing (Boddaert and Zilbovicius 2002, Wilcox et al. 2002).

A recent study by Jann et al. (2015) found frontotemporal hyperperfusion and hypoperfusion in the dorsal anterior cingulate cortex in 17 children diagnosed with

ASD and 22 matched controls, and the decreased rCBF was accompanied by increased local functional connectivity in the anterior module of the default mode network (DMN). Both alterations were associated with greater social impairments.

Gendry Meresse et al. (2005) investigated a putative relationship between rCBF of 45 children diagnosed with ASD measured at rest and their Autism Diagnostic Interview-Revised (ADI-R) scores. They found that a significant negative correlation appeared between reduced rCBF in the left superior temporal gyrus and the ADI-R score. The more severe autism, the more decreased the rCBF in that region (Gendry Meresse et al. 2005).

Possible causes of the decreased rCBF in ASD

Although the origin of this lower baseline blood flow in the autistic brain is not entirely clear, several hypotheses can be formulated. For example, it is known that inflammation or swollen tissues lead to a general increase in the pressure of the surrounding tissue, constricting blood vessels and ultimately impairing irrigation (cerebral hypoperfusion). Interestingly, exacerbated inflammatory responses were extensively documented in ASD patients, which could then be a possible cause of the observed low baseline blood flow in the brain of patients with ASD (Morgan et al. 2010, Vargas et al. 2005). A recent evaluation of the research found evidence to suggest that a majority of children with ASD have an ongoing general neuro-inflammation (Kern et al. 2015).

Also, inflammation of the endothelial lining of the blood vessels in the brain of ASD-patients has been reported. Several studies have shown vascular endothelium activation in children with ASD. Thus, upon using urinary levels of 6-keto-prostaglandin F1α as marker of endothelium activation, Yao et al. (2006) found that children with ASD had significantly higher urinary levels of this biomarker compared to controls, and ASD children were consequently presumed to suffer from some endothelial activation and/or dysfunction. Furthermore, lipid peroxidation levels directly correlated with the same vascular biomarker. The results of these investigators indicated increased oxidative stress, as well as platelet and vascular endothelial activation in the ASD patients (Yao et al. 2006).

Recent molecular research has identified genetic and epigenetic factors that can lead to, or contribute to the development of ASD (Nguyen et al. 2010, Veenstra-VanderWeele and Cook 2004). Sasaki (2015) reported that localized areas of hypoperfusion, e.g., in prefrontal lobes, cingulate gyrus, and temporal lobes, as identified by SPECT, could be caused by aberrant neuronal connectivity. The hypoperfusion could then reflect receptor, neurotransmitter or other neuronal defects (Homs et al. 2016, Huguet et al. 2013, Sasaki et al. 2015) which is analogues to the temporoparietal hypoperfusion observed on cerebral SPECT images of patients with Alzheimer's disease (Jagust et al. 2001).

Although the aberrant perfusion reported in ASD patients in some cases may have a genetic origin, environmental risk factors in ASD are important to consider, which has been pointed out by several investigators. For example, Olczak et al. (2000) reported that Thimerosal, an organomercurial additive used as preservative in some vaccines, represents a risk factor for ASD (Gallagher and Goodman 2010, Geier et al. 2014), as it could cause ischaemic degeneration of neurons in the prefrontal and temporal cortex, hippocampus, cerebellum, and pathological changes of the blood vessels in the temporal cortex in postnatally exposed rats. Other investigators have reported that mercury compounds are capable of altering vascular permeability, and thus these mercurials may be examples of environmental pollutants promoting the mechanisms leading to clinically recognizable ASD (Kempuraj et al. 2010).

Evidence of a lack of the physiological compensatory increase in cerebral blood flow in ASD patients

The brain is one of the most metabolically active organs, consuming about 20% of the available oxygen for normal functioning (Clarke and Sokoloff 1989). Therefore, a precise and timely regulation of the oxygen delivery (blood flow, perfusion, and hemoglobin affinity) is crucial for its optimal functioning and survival (Ballabh et al. 2004, Clarke and Sokoloff 1989, Hamel 2006). In a typical brain and under normal functioning, cerebral blood flow remains largely unchanged due to the basal tone of parenchymal arterioles and the contribution of large arteries to vascular resistance (Cipolla et al. 2009, Faraci and Heistad 1990). When the cerebral demands increase in an area (such as during engagement in an activity/task), vessels dilate in order to reduce resistance and increase blood flow to the area (Faraci and Heistad 1990). If blood flow does not increase to meet demand, an enhanced oxygen extraction from the blood might also aid to maintain oxygen delivery (Iadecola 1998). Clinical symptoms of ischemia are, therefore, seen only after these two mechanisms have failed to meet the oxygen demands (Hossmann 1994, Iadecola 1998). The mechanisms of auto-regulation control of the cerebral blood flow are not yet fully understood, but most evidence points towards neuronal involvement (Busija and Hestad 1984). However, the

role of nitric oxide (NO), as well as other metabolic by-products in regulating blood flow, also suggest intrinsic innervation to play a role (Paulson et al. 1990, Talman and Nitschke-Dragon 2007).

In ASD there appears to be a lack the normal compensatory increase in blood flow when engaged in a task, such as during speaking or focusing on solving a problem (Allen and Courchesne 2003, Ohnishi et al. 2000). As shown by functional magnetic resonance imaging (fMRI) blood flow increases in the brain of normal children when they engage in a task that demands attention and sensory input. This physiological response appears to be absent in children diagnosed with ASD (Müller et al. 1999). A study has shown that neurologically healthy children present a drop in the resistance of the middle cerebral artery upon auditory stimulation, which indicates that the artery relaxes and blood flood flow increases, delivering more oxygen to this part of the brain. Conversely, upon the same stimulus, the resistance in the middle cerebral artery increased in children diagnosed with ASD, indicating that the artery contracts and thereby limits blood flow and oxygen delivery (Bruneau et al. 1992). The origin of this lack of the compensatory response (increased blood flow) upon a stimulus in the autistic brain is unknown, but it is likely to be related to an absence of the signal/receptor involved in vasodilatation in the brain (Ohnishi et al. 2000).

As mentioned, children diagnosed with ASD have abnormal rCBF in the bilateral insula, superior temporal gyri and left prefrontal cortices (BA 9/45) compared with the non-autistic controls. Ohnishi et al. (2000) suggested that these abnormal areas are related to the cognitive impairments observed in children diagnosed with ASD, such as deficits in language, impaired executive function and abnormal responses to sensory stimuli. Disturbance in the perception and modulation of sensory information is often observed in ASD patients. Several studies suggest that the insular cortex should be connected to a variety of paralimbic systems and heteromodal association areas that are important in processing complex sensory information (Augustine 1996). Dysfunction in this area due to hypoperfusion could cause abnormal responses to sensory stimuli because of the abnormal integration of sensory stimuli. Frontal and temporal abnormalities in ASD have also been demonstrated in EEG studies and other SPECT studies (Dawson et al. 1995, Mountz et al. 1995).

Consequences of the hypoperfusion

It is well known that oxygen is crucial to life as it is involved in the generation of cellular energy (ATP) and therefore fueling all cellular functions. The mammalian brain is in fact very sensitive to hypoxia, and it is one of the first organs to fail during oxygen limitations. Most of the deleterious processes under suboxic conditions are directly or indirectly triggered by the inability of the mammalian brain to maintain the required ATP levels (Allen and Courchesne 2003). In fact, several studies (Araghi-Niknam and Fatemi 2003, Fatemi et al. 2001, Fatemi and Halt 2001, Nguyen et al. 2010, Sheikh et al. 2010), have demonstrated a decrease in Bcl-2 which is associated with increased apoptosis (cell death) in autistic brains (Shimizu et al. 1996). Therefore, proper brain oxygenation is a prerequisite not only for survival but also for optimum functioning. Thus, irrespective of the basic cause of the hypoperfusion in cerebral areas of ASD patients, the diminished blood flow indicates that oxygen limitations might be the explanation of at least some of the symptoms present in ASD patients (Ohnishi et al. 2000).

Furthermore, it has been shown that ASD patients have elevated levels of vascular endothelial growth factor (VEGF) in their cerebrospinal fluid. VEGF is produced by various cells under hypoxia, e.g., by vascular endothelial cells and macrophages (Brogi et al. 1996, Namiki et al. 1995, Prandota 2010, Vargas et al. 2005), indicating some degree of cerebral hypoxia in ASD patients. VEGF production might aim to improve diffusion of irrigation, as it was demonstrated that chronic exposure to VEGF leads to the appearance of small 'holes' within the endothelium, associated with improved microvascular permeability of vital substances including NO and prostacyclin (Dobrogowska et al. 1998, Murohara et al. 1998, Roberts and Palade 1995).

Possible treatments

Although there are no established treatments for hypoperfusion in ASD, there are some studies and anecdotal reports of treatments that deserve a proper evaluation. Carnitine, for example (Hülsmann and Dubelaar 1992), a naturally occurring amino acid required for energy metabolism, may be useful. Vascular endothelial cells are more vulnerable to oxidative stress and are prone to lose carnitine early during hypoperfusion. In rats, L-carnitine supplementation reduced lipid peroxidation and oxidative DNA damage and enhanced oligodendrocyte marker expression and myelin sheath thickness in cases of chronic hypoperfusion (Ueno et al. 2015). Also, in humans, carnitine administration was observed to increase significantly brain blood flow (Battistin et al. 1989, Postiglione et al. 1992, 1999). The replenishment of the carnitine that is reduced by hypoperfusion in ASD may be the reason for the reports of improved cognition in children

diagnosed with an ASD treated with carnitine (Fahmy et al. 2013, Geier et al. 2011).

Cilostazol, a quinolinone derivative medication that enhances the flow of blood and is used in the alleviation of the symptom of intermittent claudication in individuals, may also be helpful. Chronic hypoperfusion causes disintegration of white matter and is characterized by neuroinflammation, loss of oligodendrocytes, and attenuation of myelin density (Choi et al. 2016). However, in rats with chronic hypoperfusion, Cilostazol protected against white matter disintegration and cognitive impairments (Choi et al. 2016). Anecdotal reports suggest that children diagnosed with an ASD have improved cognition when treated with Cilostazol.

Although the results were mixed (Bent et al. 2012, Jepson et al. 2011, Rossignol et al. 2007, 2012, Sampanthavivat et al. 2012), it has been suggested that hyperbaric oxygen therapy (HBOT) might be used to compensate for the decreased blood flow in ASD patients, by increasing the oxygen content of blood plasma and body tissues (El-Baz et al. 2014). For example, Zádori et al. (2011) examined the survival and differentiation of neuroectodermal cells with stem cell properties at different oxygen levels and found that lesioned cortices under hypoxia (low oxygen levels) were partially corrected by HBOT. In a randomized study of 30 ASD children, Vecchione et al. (2016) reported significant improvements in visual perception, motor coordination, stereotypic behavior, hyperactivity, inappropriate speech and general communication ability after repeated sessions of low-pressure hyperbaric oxygen.

Although long-term use of the traditional antipsychotic agent Risperdal (risperidone) can have serious side effects such as precipitation of a potentially permanent movement disorder (tardive dyskinesia), research suggests that it can reduce problematic behaviors in autistic children (Kirino 2014) and improve brain perfusion. And risperidone has been reported to improve brain perfusion. Ozdemir et al. (2009) followed 11 ASD patients (6–7 years of age), who received risperidone therapy for three months. SPECT imaging demonstrated a relationship between clinical improvement and regional perfusion patterns after risperidone treatment. However, considering that Risperdal (risperidone) has potentially fatal side effects, the risk to benefit ratio should be thoroughly evaluated before initiating this treatment.

Electro-acupuncture also shows promise. Electro-acupuncture was evaluated in 55 children diagnosed with ASD using SPECT (Zhao et al. 2014). They found that after treatment, there were significant differences in the ratios of rCBF and global CBF before and after treatment in the left and right prefrontal cortex, the left and right temporal lobe, and in the left Broca's area. Also, the treated children exhibited symptomatic relief.

CONCLUSION

Cerebral hypoperfusion is consistently observed amongst individuals diagnosed with ASD, and evidence suggests that it plays an important role in the pathophysiology and that the hypoperfusion also reflects the autism severity. The basic cause of this hypoperfusion may involve genetic, epigenetic, environmental or a composed set of factors. However, the evidence outlined in this review of the literature emphasized that hypoperfusion is a critical issue in ASD and that addressing this could represent important steps in attempts to arrest pathophysiological deterioration and also help to alleviate the symptomatology in individuals diagnosed with ASD.

A possible weak point of this study is the need to review the topic through a meta-analysis investigation, in order to retrieve a wider and deeper focus on the issue. Actually, in a more general way, the best approach to show the significant hypo-perfusion in autistic brain is to run a meta-analysis on data from all published articles on that topic (Haidich 2010). In this sense, a meta-analysis of the imaging in ASD is a next forthcoming target of the investigation.

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