Nervenarzt 2016 · 87 (Suppl 2):S55–S61
DOI 10.1007/s00115-016-0172-3
Published online: 16 August 2016
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L. Liu[1] · D. Zhang[1] · J. K. Rodzinka-pasko[2] · Y.-M. Li[1,3]

[1] Xiangya Nursing School, Mental Health Institute of the Second Xiangya Hospital, Central South University, Changsha, PR China

[2] Division of Applied Medicine, University of Aberdeen, Aberdeen, UK

[3] Clinical Nursing Teaching and Research Section, the Second Xiangya Hospital, Central South University, Changsha, PR China

Environmental risk factors for autism spectrum disorders

Introduction

Autism spectrum disorders (ASD) are characterized by impaired social interactions, communication deficits, and restricted interests or repetitive behaviors, and have been often classified among childhood schizophrenia or attention deficit hyperactivity disorder (ADHD) in the past. They are typically diagnosed by the early developmental period based on the guidelines established by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) [1]. The worldwide average incidence of ASD is around 0.62–0.70 %, according to the latest reports [2]. In the past few decades, the reported prevalence of ASD has increased. However, this growth can be partially explained by an increased awareness of the problem among professionals and by better diagnostic methods [3]. ASD are generally classified as neurodevelopmental disorders, evidenced by atypical structural and functional brain development [4]. Nevertheless, no causative factors have been established so far. Genetic factors (e.g., genetic predisposition, or spontaneous mutations), early damage/immaturity of the brain (in premature babies) [5], environmental factors [6], or different combinations of the above have all been suggested to play a major role in the pathogenesis of ASD. This would imply the existence of various clinical phenotypes of ASD resulting from diverse causes, rather than from a single causative factor. It was reported that environmental factors can interact with susceptibility genes for ASD, and through epigenetic changes may lead to alterations in gene expression, transgenerational epigenetic inheritance, or both [7]. In this paper, we review recent studies on environmental risk factors for ASD.

Reference citation criteria

Literature included in this review has fulfilled the following criteria: (a) The content of the reported studies was related to the environmental risk factors of autism spectrum disorders and (b) the article was published in a peer-reviewed journal after 1995.

Electronic searches of the PubMed database were conducted using keywords including: autism spectrum disorders, air pollution, environmental toxicants, seasonal factors, psychological stress, migration, birth order, gender, nutritional factors etc. Further, the reference sections of the already included literature were examined to identify possible additions to the review. A total of 76 articles were identified that fulfilled the inclusion criteria.

Natural environmental factors

Air pollution

In recent years, many studies have associated air pollution with the occurrence of ASD [8, 9]. Traffic-related air pollutants such as polycyclic aromatic hydrocarbons (PAHs) and some of the inhalable particulate matter such as PM 2.5 and PM 10 are a risk factor for the onset of ASD, especially if the exposure occurs during the late stages of the mother's pregnancy or in the first year of the newborn's life [9]. The specific pathological mechanisms can be explained by toxicology and genetics studies. A study by Perera et al. reported that diesel exhaust particulate (DEP) and PAHs can affect the brain's functions and activities [10]. Another study reported that children exposed to high levels of carbon monoxide, nitrogen dioxide, ozone, or sulfur dioxide during the early developmental period are at higher risk for ASD [8]. The possible pathophysiologic mechanisms may involve oxidative stress and inflammation. Oxidative stress can lead to ASD by increasing the levels of lipid peroxide and nitric oxide, reducing antioxidant activity, and triggering inflammation [11]. Short- or long-term exposure to high concentrations of ozone can induce oxidative stress, leading to brain lipid peroxidation that causes neuronal structural damage [11]. Hemoglobin has a higher affinity for carbon monoxide than for oxygen; therefore, hypoxia due to carbon monoxide exposure can cause muscle, tissue, brain, and nervous system damage [12]. Long-term exposure to high concentrations of nitrogen dioxide can induce chronic lung inflammation and even systemic inflammation [13]. Numerous studies reported that inflammation or maternal immune activation can increase concentrations of certain cytokines (e. g., interleukin [IL]-6, tumor necrosis factor [TNF]). Measured IL-6 concentrations were found to be significantly higher in children with ASD than

in children without ASD [14, 15]. Hence, it has been suggested that although the underlying mechanisms are not clear, the inflammation during pregnancy may be correlated with the prevalence of ASD in the offspring [14, 15]. A recent animal study revealed that IL-17 may be a key link between inflammation or maternal immune activation and ASD. The findings suggest a mechanism whereby in infected mice with a higher concentration of cytokine IL-6, activated TH-17 cells secrete pro-inflammatory cytokine IL-17, which damages the fetal brain. As a result, the offspring present with a behavior similar to the abnormal behavior observed in autism. Moreover, it was demonstrated that when TH-17 cells in the pregnant mice were inactivated, and the inflammation induced afterwards, the offspring did not exhibit abnormal behavior. What is more, treatment of the infected pregnant mice with anti-IL-17, a blocking antibody, was shown to have a potential ameliorating effect on ASD-like behavioral abnormalities in the mouse pups [16]. Finally, exposure to sulfur dioxide can reduce the activity of superoxide dismutase (SOD), glutathione (GSH), and glutathione peroxidase (GSH-PX) – enzymes regulating the intracellular level of free radicals – thus leading to lipid peroxidation and brain damage [17].

Environmental toxicants

In recent years, many studies reported that some environmental toxins such as heavy metals and some organic compounds are associated with the onset of ASD. However, there is still much debate over the potential pathophysiological correlation between environmental toxicants and ASD. Goines and Ashwood speculated that the susceptibility genes of ASD can increase an individual's sensitivity to the effects of environmental toxicants, thereby increasing the risk of ASD [18]. Environmental toxins can damage neuronal electrical or chemical signal conduction, causing nerve dysfunctions. Some environmental toxins can also disrupt the endocrine system and cause abnormal maternal immune responses, eventually leading to the onset of ASD. LaSalle et al. proposed that environmental toxins such as heavy metals can affect the level of DNA methylation and increase the risk of ASD [19]. A recent meta-analysis also correlated the severity of ASD with the levels of heavy metals in the blood, urine, and hair of patients with ASD [20], and it suggested a dose-dependent effect of heavy metal levels.

Heavy metals

Multiple studies demonstrated that long-term exposure to environmental heavy metal pollution (e. g., arsenic, cadmium, lead) during pregnancy and the first year of life is likely associated with the incidence of ASD [20, 21]. Heavy metals with immunotoxicity may lead to the production of autoantibodies and to the abnormal secretion and activation of cytokines. Exposure to this harmful environment during this critical period may disrupt the development of the nervous and immune systems, resulting in the onset of ASD or other nervous system, behavioral, or immune system disorders [18]. Lead and mercury are known causes of neurodevelopmental disorders [21]. The study by Blanchard et al. reported a close correlation between high concentrations of mercury in the environment and the incidence of ASD [22]. Mercury can significantly increase the intracellular calcium content and can also interfere with the immune system functions. Increased levels of IL-6 and autoimmune response were observed in mice after the animals were exposed to high levels of mercury [18]. Lead is not only a neurotoxin, but it can also affect the immune system. In fact, high levels of lead in the body can inhibit the immune response, thus increasing the chances of infections, whereas low concentrations of lead can stimulate it [18]. A case-control study reported that the mothers of children with ASD were more frequently exposed to lead during their pregnancy than the mothers of unaffected children; however, the sample size was limited, and additional research is needed to confirm this finding [23].

Organic toxicants

Since the 1960s, many organic compounds widely distributed in the environment have been identified as toxicants in animals and humans. Some organic pollutants were proved to have adverse effects on neurodevelopment. Recent studies found that the children of women who, because of their occupation, were exposed during their pregnancy to paint, varnish, asphalt, or other solvents containing xylene were more likely to be affected by ASD [24]. Some organic poisons called endocrine disruptors or endocrine-disrupting chemicals (EDCs) can interfere with the endocrine system and increase the risk of ASD. Experiments in mice showed that low thyroid hormone levels can inhibit the growth of cerebellar Purkinje cells [25], and abnormalities in the Purkinje cells of individuals affected by ASD have also been reported. Therefore, an abnormal level of thyroid hormone during pregnancy is considered a potential factor in the etiology of ASD.

Pesticides

Pesticides often target the nervous system. Some pesticides have been classified as persistent organic pollutants (POPs) and some are also EDCs [26]. Most Western countries have reduced the use of organochlorine pesticides, but some pesticides are still occasionally used. A study conducted in a community of farm workers reported a high prevalence of pervasive developmental disorder (PDD), and correlated it with a high concentration of pesticides in the urine of pregnant women [27]. Similarly, in another study conducted in a community in the state of New York, the concentration of pesticides in the umbilical cord blood was associated with PDD symptoms [28]. In neuroimaging studies, Rauh and colleagues showed changes in the volume of cerebral cortex areas related to language and social cognition in children with high levels of chlorpyrifos (a pesticide) in umbilical cord blood [29]. Pesticides can affect neural development through a variety of mechanisms. The study by Roberts and English also reported that the two time periods most vulnerable to the effects of pesticide exposure are (a) between 38 days before fertilization and 163 days after and (b) between 346 and 529 days after fertilization [30].

Phthalic acid

Phthalic acid is often used in cosmetics, lotions, perfumes, and also building materials; it can inhibit the production of androgen hormones and may be correlated with the onset of ASD [31]. Studies showed that high levels of phthalic acid metabolites are associated with reduced physical development and growth [32], behavioral or attention problems, and social dysfunction in children [33]. A recent study found that the presence of ethylene in the flooring of children's and parents' bedrooms was closely correlated with ASD in the children [34]. Moreover, flooring materials containing PVC can release phthalates and PVC an important source of phthalates in the air. A prospective study by Miodovnik et al. showed that the children of women who had high levels of phthalates in their urine while pregnant were more likely to present social problems [33].

Seasonal factors

The risk of ASD onset significantly varies according to what time of the year the pregnancy occurred, as many recent studies reported. Zerbo et al. studied 6.604.975 healthy children and 19.238 children with ASD born in California between 1990 and 2002 by comparing the season when their mothers' pregnancy started [35]. The results revealed that ASD incidence was 6 % higher among children whose mothers were pregnant during winter (December, January, and February) compared with the incidence in children whose mothers were pregnant during summer (June, July, and August) [35]. Another study found that children born in March and August were more likely to suffer from ASD [36]. A large-sample Danish study from 2010 found that severe influenza, viral gastroenteritis, and urinary tract infection in women during their pregnancy constitute risk factors for ASD. Namely, severe viral infections in early pregnancy may increase the risk of ASD by 2.98 times, and severe bacterial infections in the middle of pregnancy may increase the risk of ASD by 1.5 times [37]. Atladottir et al. found that children born in summer were more likely to suffer from ASD because the first 3 months of their mothers' pregnancy constituted a period of increased risk for viruses or other infections [38]. Meta-analyses also reported that being born in summer is a risk factor for ASD [39]. Gadow and DeVincent observed that the ASD phenotype of children with ASD born in summer is more severe [40]. Different mechanisms could explain these results; when the first trimester of pregnancy occurs in winter, chances for maternal infections are higher [38], daylight time is shorter, and the seasonal availability of food changes, leading to potential deficiencies in vitamins or other nutritional elements [39]. Further research will

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Environmental risk factors for autism spectrum disorders

Abstract

Background. Autism spectrum disorders (ASD) are syndromes that are predominantly defined by behavioral features such as impaired social interactions, restricted verbal and nonverbal communication, and repetitive or stereotyped behavior. In the past few decades, the reported prevalence of ASD has increased dramatically. This growth can be partially explained by an increased level of awareness of the problem among professionals and better diagnostic methods. Nevertheless, underpinning causes of ASD have not yet been detailed and explained. It is suggested that rather than having a single causative factor, ASD pathogenesis is influenced by environmental or genetic factors, or a combination of both. The aims of this review are to describe the environmental risk factors associated with ASD so as to provide a reference basis for current and future clinical and experimental work.
Materials and methods. On the basis of a PubMed search, we review the existing knowledge on environmental factors associated with ASD.
Results. A series of environmental factors have been repeatedly reported as risk factors for ASD in existing studies.
Conclusion. Air pollution, organic toxicants, seasonal factors, psychological stress, migration, birth order, and nutrition may have a close relationship with the incidence of ASD.

Keywords

Autism spectrum disorder · Risk factors · Environment · Air pollution · Migration

Umweltrisikofaktoren für Autismusspektrumstörungen

Zusammenfassung

Hintergrund. Autismusspektrumstörungen (ASS) sind überwiegend durch Verhaltensmerkmale definierte Syndrome, wie eingeschränkte soziale Interaktion, begrenze verbale und nonverbale Kommunikation und repetitives oder stereotypes Verhalten. In den letzten Jahrzehnten stieg die gemeldete Prävalenz von ASS drastisch an. Dieser Anstieg ist z. T durch ein vermehrtes Bewusstsein für diese Erkrankungen bei den damit befassten Berufsgruppen und durch bessere diagnostische Verfahren zu erklären. Trotzdem wurden die zugrunde liegenden Ursachen von ASS bisher nicht detailliert aufgeführt und erklärt. Es gibt Hinweise darauf, dass anstelle eines einzelnen ursächlichen Faktors die Pathogenese von ASS eher von Umwelt- oder genetischen Faktoren oder einer Kombination aus beiden beeinflusst wird. Ziel der vorliegenden Übersichtarbeit ist die Beschreibung der Umweltrisikofaktoren im Zusammenhang mit ASS, um eine Referenzgrundlage für laufende und zukünftige klinische und experimentelle Arbeiten zu schaffen.
Material und Methoden. Auf der Grundlage eine PubMed-Suche wird ein Überblick über das vorhandene Wissen zu Umweltfaktoren gegeben, die mit ASS in Zusammenhang stehen.
Ergebnisse. Eine Reihe von Umweltfaktoren sind wiederholt als Risikofaktoren von ASS in bestehenden Studien genannt worden.
Schlussfolgerung. Luftverschmutzung, organische Giftstoffe, saisonale Faktoren, psychischer Stress, Migration, Geburtenfolge und Ernährung können in engem Zusammenhang mit der Inzidenz von ASS stehen.

Schlüsselwörter

Autismusspektrumstörung · Risikofaktoren · Umwelt · Luftverschmutzung · Migration

be needed to explore the mechanisms underlying these correlations.

Social and familial environmental factors

Psychological stress

A large number of studies reported that psychological stress during pregnancy and the early stages of life of the newborn [41] is linked to ASD. Beversdorf et al. claim that weeks 21–32 of gestation are a critical stage in the development of the baby's cerebellum, and if the mother suffers from stress, this may increase the risk of ASD in the offspring [42]. Kinney et al. propose that children suffering from severe stress in their first 6 months of life are at increased risk of ASD [43]. Franklin et al. showed that mouse pups who chronically experienced sudden maternal separation (a stress factor) presented depression symptoms and negative responses to the introduction of new stimuli in the environment when adult. Maternal separation also changed the DNA methylation profile of several promoters of genes regulating reproduction. Similar changes in DNA methylation were also found in the brain of the offspring of mice who experienced maternal separation as pups [41]. Various mechanisms can explain these results; for example, stress can stimulate mast cells to release inflammatory and neurotoxic cytokines and increase the serum levels of corticotropin-releasing hormone (CRH) [44]. The combined effects of CRH and activated mast cells can change the permeability of the blood–brain barrier, allowing neurotoxic cytokines to cross it into the brain, activate glial cells, cause inflammation of the brain, and increase the risk of ASD [45].

Migration

Migration has become a common worldwide social phenomenon, attracting scientific investigation. Researchers found that maternal immigration (i. e., the child's mother is an immigrant) is a potential risk factor for ASD [46], and ASD incidence in families who migrated to the Nordic region was higher than in indigenous families [47]. Magnusson et al. reported that children whose parents moved to Sweden from regions with a low human development index had increased risk of ASD [48]. Low immunity against common infections or high levels of stress in the mother may be underlying mechanisms [49]. Moreover, immigrant families may have limited social interactions because of cultural differences or language barriers, and this situation can also negatively affect the children's cognitive and behavioral development. Once again, further studies will be required to explore the correlation between migration and ASD.

Birth order

Multiple studies reported a correlation between ASD and birth order [39, 50]. Chaste and LeBoyer showed that ASD incidence in later-born children was significantly higher than in first-borns [39, 50]. Zwaigenbaum et al. found that later-born children were more frequently afflicted by prenatal, perinatal, and neonatal complications [51]. Martin and Horriat reported that ASD prevalence among second-born children was higher than among first-borns, especially when the siblings were born less than 24 months apart; moreover, the verbal and nonverbal IQ scores of second-born autistic children were significantly lower than those of autistic first-borns [50]. The specific mechanisms are unclear and may include the parents' ages when the child was conceived (and thus the likelihood of de novo mutations in the offspring) [52] and environmental or immune factors [50]. Environmental factors such as the amount and quality of parental care also affect the child's cognitive development; because the first child receives all of the parental attention without sharing it with other siblings, ASD symptoms in first-borns are usually less severe than the symptoms observed in second-born children [53]. Further research will be required to clarify these results.

Gender

ASD are more prevalent in males. Early studies demonstrated that ASD affect 4–5 times more males than females [54], while several large-scale, population-based studies have shown that there are 2–3 times more males than females affected [55]. Nevertheless, factors responsible for the higher prevalence of ASD in males remain unclear. Some researchers have speculated that certain biological factors may be partially responsible for this gender difference in ASD [56]. For instance, the extreme male brain theory of ASD, which extends the empathizing–systemizing (E-S) theory of typical male bias, proposes that males' and females' brains differ in terms of their characteristics. That is, on average, males tend to be better at analyzing systems (better systemizers), while females tend to be better at reading the emotions of other people (better empathizers) [56]. On the empathy quotient (EQ), the score of a typical female is higher than that of a typical male, who on the other hand, scores higher than people with ASD. By contrast, individuals with ASD score higher on the systemizing quotient (SQ) than typical males do, who in turn score higher than typical females [57]. It may suggest that there are some potential protective factors present in females, and that the criteria for the diagnosis are specifically targeted at males. In contrast to classic autism, which requires intellectual disability to be diagnosed and hence is unlikely to be missed, ASD may be under-diagnosed among females [56]. Empirical data show that there are fewer highly functioning females meeting diagnostic criteria for ASD compared with males [58]. In conclusion, two factors seem to be emphasized in explaining gender differences in ASD prevalence. First, male-specific risk factors that increase their susceptibility to develop the disorders. Second, the observation that females may need to present with more substantial behavioral or cognitive problems for the diagnosis to be warranted. Therefore, greater efforts should be invested in the study of ASD etiology (genetics, environment, etc.) in females.

Nutritional factors

A study by Dionne et al. showed that the pathogenesis of ASD may begin before birth [59]. An abnormal metabolism of the mother during pregnancy may be linked to neurological and behavioral disorders and ASD in the newborn [60]. Moreover, studies showed that omega-3 fatty acids, probiotics, vitamins A, B_6, B_{12}, C, and D, folic acid, magnesium, iron, and other dietary supplements can improve ASD symptoms [61].

Fatty acids

Fatty acids are important biomolecules for normal human growth and development; in particular, omega-3 fatty acids are essential for normal fetal brain development. Nevison et al. found that the risk for ASD was higher among the children whose mothers had low amounts of omega-3 fatty acids in their diet during their pregnancy [3]. Lyall et al. also argued that an appropriate intake of fatty acids during pregnancy is a protective factor against ASD and is closely correlated with ASD incidence in the offspring [7]. Kawicka and Regulska-Ilow reported that an insufficient intake of omega-3 fatty acids can lead to abnormal neurological and cognitive development in children, characterized by concentration deficits, hyperactivity, dyslexia, movement disorders, and ASD [61]. De Felice et al. found that adding omega-3 fatty acids to the diet can alleviate the acute-phase symptoms of Rett syndrome [62]. Another study reported that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplements improved autistic children's language and social communication abilities and also relieved some ASD symptoms such as excessive fear or excitement [63]. Although the specific mechanism underneath the effects of fatty acids is still unclear and additional investigations are needed, pregnant women should be encouraged to eat an adequate amount of fatty acids to reduce the risk of ASD in their babies.

Vitamin D

Vitamin D plays a key role in maintaining human health. In recent years, several studies reported that vitamin D deficit during pregnancy is a risk factor for ASD, and an adequate vitamin D intake during pregnancy can reduce the risk of ASD [64]. Whitehouse et al. found that maternal vitamin D deficits may cause speech and language problems and attention disorders in the offspring [65]. The sun's ultraviolet rays can help skin synthesis of vitamin D, which is the main source of human vitamin D. Whitehouse et al. reported that ASD prevalence was higher in regions with frequent rainy days like the states of Oregon, Washington, than in sunnier areas[65]. Although the specific mechanisms are not completely understood, vitamin D has important roles in the differentiation of neurons and the metabolism of toxins; it also helps in protecting the brain, preventing inflammation, regulating the endocrine system, and promoting fetal brain development [7, 64]. Thus, vitamin D deficits in early pregnancy may affect the baby's brain development and increase the risk of ASD. Further research will be required to find direct evidence of the correlation between vitamin D deficiency and ASD and its pathological mechanisms.

Folic acid

Folic acid has an important role in cell mitosis, and therefore it is very important for pregnant women [66]. A large number of studies demonstrated that if pregnant women have a sufficient amount of folic acid in their diet, the risk of neural tube defects [66], ASD, and other neurodevelopmental disorders [19, 67] in the baby is reduced. Moreover, folic acid deficit during pregnancy may increase the risk of ASD. Suren et al. reported that the mothers of children with ASD had a lower amount of folic acid supplements during the first month of their pregnancy compared with the mothers of healthy children [68, 69]. Ramaekers et al. found that the folic acid content in the cerebrospinal fluid (CSF) of patients with ASD was significantly lower than the level observed in children with a typical development [70]. Folic acid plays an important role in the patterns of DNA demethylation and re-methylation in the embryo [71]. Folic acid participates in the transfer of carbon units and in DNA synthesis and methylation by providing a methyl group, and thus it contributes to maintaining genomic stability, which may be the connection between folic acid and ASD [68].

Mineral deficiencies

A recent study reported that deficiencies of minerals such as zinc and magnesium in the mother are likely to be a risk factor for ASD in the child [63]. Nearly 30 % of children with ASD have zinc and magnesium deficits [61, 72]. Arnold et al. found that the average zinc serum level in children with ASD and ADHD was significantly lower than the value observed in healthy children, and it correlated with ADHD children's attention deficits [73]. In addition, treatment with zinc dietary supplements can effectively improve ADHD symptoms such as impulsive behavior and social interactions difficulties [74]. Zinc is an important trace element and plays key roles in nucleic acid and protein syntheses, cell mitosis, and tissue growth and repair. Zinc deficiency is associated with various conditions including taste disorders, delayed wound healing, impaired immune response, delayed growth and physical development, and neurodegenerative diseases in children [73]. Zinc deficiency can also affect the excretion of toxic metals such as cadmium and lead, thereby increasing their accumulation in the body [75]. Thus, zinc deficiency in infants can lead to higher concentrations of toxic metals in the body and increase the risk of ASD [72]. Mousain-Bosc et al. reported that the level of magnesium in the red blood cells of children with ASD was below normal values. After treatment with magnesium and vitamin B_6 supplements, magnesium levels within red blood cells increased, and the patients' clinical symptoms improved [76]. Therefore, the analysis of trace elements may be an important tool in the early screening and prevention of neurodevelopmental disorders and ASD.

Conclusion and perspectives

In conclusion, environmental factors including air pollution, organic toxicants, seasonal factors, psychological stress, migration, birth order, gender, and nutrition may have significant links to ASD. In the past few decades, major advances were made in this research field, but many questions remain unanswered. Further research will be required to understand whether environmental factors alone can cause ASD or whether they do so through complex interactions with other factors. Future studies should also clarify the specific pathophysiological mechanisms underlying the correlations between the single environmental factors and ASD.

Corresponding address

Dr. Y.-M. Li
Clinical Nursing Teaching and Research Section, the Second Xiangya Hospital, Central South University
139 Middle Renmin Road, 410011 Changsha, PR China
amin5433@163.com

Compliance with ethical guidelines

Acknowledgments. This work was supported by the Fundamental Research Funds for the Central Universities of Central South University (grant number: 2015zzts290).

Conflict of interest. L. Liu, D. Zhang, J.K. Rodzinka-pasko, and Y.-M. Li state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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