International Journal of Immunopathology & Pharmacology

Original Research Article

Childhood atopic dermatitis as a precursor for developing attention deficit/hyperactivity disorder

International Journal of Immunopathology and Pharmacology
Volume 34: 1–10

DOI: 10.1177/2058738420962902
journals.sagepub.com/home/iji
SAGE

Yang-chun Xu[1], Jin-peng Wang[2], Wen-jing Zhu[1] and Ping Li[3]

Abstract

Atopic dermatitis (AD) is a skin disease characterized by chronic inflammatory condition that shows hallmark presentations in terms of sleep disturbances, pruritus, and psychological stress, and an association with increased attention deficit/hyperactivity disorder (ADHD) risk. A number of studies have suggested for the co-occurrence of the two diseased conditions. In terms of global prevalence, AD and ADHD almost exhibit a parallel increment according to epidemiological data. In addition, recent reports indicate AD to show a temporal association with later onset of ADHD. Although several studies suggest for the potential link between AD and ADHD, currently there is no definitive answer to this regard. Furthermore, epidemiological evidence of co-occurrence does not ascertain a pathophysiological link between the two conditions. The pathophysiological basis behind the association of AD and ADHD also remain poorly elucidated. The objective of this review is to present an extensive account of AD and associated comorbidities with a special attention toward ADHD as well as to elaborate on the mechanisms underlying their association. The review can provide healthcare providers with the recent updates on AD-ADHD association and help them while dealing with such patients. In general, AD and ADHD show a positive association in majority of the cross-sectional studies. However, large longitudinal studies are required to draw any conclusion on the temporal nature of such association.

Keywords

atopic dermatitis, atopic diseases, attention deficit/hyperactivity disorder, eczema, psychiatric comorbidities

Date received: 28 June 2020; accepted: 8 September 2020

Introduction

Atopic dermatitis (AD) is the presentation of a complex diseased condition ever challenging the scientific world with regard to its clinical phenotype and its origin. It is usually an inflammatory disorder of the skin with recurrent intense itch and eczematous lesions.[1] In 1933 Wise and Sulzberger coined the term AD,[2] which has evolved over the years. In recent times, attempts were made to redefine AD as per immunologic pathomechanisms, genetic findings as well as epidemiological insights underlying the condition. Nearly 15–20% of children get affected by AD all over the world.[3] Among such children, two/thirds present themselves by the age of 2 years and the rest by the age of 5 years.[4] AD is a complex heterogeneous condition presenting itself with varying symptoms (e.g. anxiety, depression, sleep disturbance and pain), persistence (e.g. persistent, intermittent, transient), distributions (e.g. trunk, hands, head and

[1]Department of Dermatology, the Second Hospital of Jilin University, Changchun, Jilin, China
[2]Department of Cardiology, the Second Hospital of Jilin University, Changchun, Jilin, China
[3]Department of Developmental Pediatrics, the Second Hospital of Jilin University, Changchun, Jilin, China

Corresponding author:
Ping Li, Department of Developmental Pediatrics, the Second Hospital of Jilin University, 218 Ziqiang Street, Nanguan District, Changchun, Jilin 130041, China.
Email: l_ping@jlu.edu.cn

neck, flexural, extensor), signs (e.g. lichenification, oozing/weeping, erosions, xerosis, plaques, papules, follicular accentuation, lichenoid papules, prurigo nodules).[2,3] Big data reveal increase in AD burden with several comorbidities, both cutaneous[5] and systemic ones[6,7] AD shows itself with dysfunctioning immune and non-immune skin-barrier components. AD patients have a low compliance with long-term therapies and that may be due to the underrecognized psychiatric burden[8] occasionally relapsing for different stressful conditions such as COVID-19 outbreak.[9]

Not only impulsive behaviors and above-normal hyperactive levels but also inattention are regarded as attention deficit/hyperactivity disorder (ADHD). ADHD-challenged people face problem of focusing on a single job for prolonged periods. Since the 1980s, the association between allergic diseases and ADHD, whether rooted in causality or comorbidity, is a cause of both clinical and public concern.[10] It is estimated that nearly 7.1% of children and adolescents show symptoms of ADHD worldwide.[11] Early-school children show patterns of ADHD with persistent hyperactive-impulsivity and inattention that influences either or both of social development and functioning, with the symptoms often persisting till adulthood.[4] There are a number of therapeutic interventions such as medications, cognitive training or behavioral therapy for children suffering with ADHD. However, the success of such therapies depend a lot on the individual getting treated since a number of factors (both environmental and genetic) greatly influence their behavioral patterns during development.[4,12] A number of reports suggesting for allergic conditions in ADHD children is a cause of great concern among healthcare practitioners. However, whether ADHD is associated with immune hypersensitivity is not fully understood. There is evidence for allergic manifestations (e.g. asthma or atopic dermatitis) as a result of both non-stimulant and stimulant treatments in ADHD; however, the reasons behind such allergic manifestations have remained largely elusive.[13–15]

As early as 1975, it was postulated that components of food that give rise to atopic response as allergens may also result in hyperactivity development.[16] Therapeutic benefits were evidenced for children with ADHD when provided with hypoallergenic diet.[17] A number of hypotheses have been provided with regard to the underlying mechanism relating AD and ADHD. In addition to comorbidities of both diseases, allergic inflammation causing increased cytokine release may impact precise locations in the neurotransmitter systems and prefrontal cortex, eventually playing a role in ADHD pathology.[18] A number of cross-sectional studies established an association between ADHD and other atopic diseases (i.e. allergic rhinitis, atopic eczema and asthma) over the past decade.[19–21] ADHD is often preceded by atopy thereby giving validity toward the reasoning of atopy as the cause of ADHD onset. However, any conclusion on the temporal nature of such association warrants caution in absence of prospective longitudinal data. Till now, ADHD and atopy in general show a positive association in majority of the cross-sectional studies.[20,22]

The objective of this review is to present an extensive account of AD and associated comorbidities with a special attention toward ADHD as well as to elaborate on the mechanisms underlying the association between AD and ADHD.

Hypotheses behind AD pathophysiology

There are two major hypotheses underlying AD pathophysiology:

Outside-in: Outside-in hypothesis proposes for a compromised complex matrix consisting of epidermal proteins, and/or lipids, epidermal keratinocytes resulting in exposure of the epidermis to reduced skin hydration, transepidermal water loss (TEWL), and other external insults, causing inflammation and immune deregulation.[23] As compared to healthy controls, AD patients with lesional skin show up with significantly compromised barrier function. Furthermore, non-lesional skin or previously inflamed skin also shows dysfunctioning barrier.[24] Increased TEWL owing to decreased osmotic draw is caused due to impaired profilaggrin cleavage and a consequent decrease in natural moisturizing factors (NMFs).[25] Besides NMFs, skin surface pH is decreased by other acidic metabolites that include free fatty acids.[26] It is important to have an acidic skin pH (4–6) for proper confirmation and expression of proteins of epidermal origin,[27] enzyme activation (e.g. lipases) and inhibition (e.g. proteases), crucial for non-pathogenic skin flora[28] and barrier function regulation.[29] Both non-lesional and lesional skin in AD patients shows

significantly higher pH.[30] Tight junction functional impairment has been found in AD patients, resulting in dysfunctional skin barrier.[31,32] Multiple environmental and external factors including airborne pollutants,[33,34] harsh climate,[35] tobacco smoke,[36] contact allergens,[37] water hardness,[38] bacterial dysbiosis,[39] utero exposures,[40] and personal care products (i.e. pruritogens and irritants)[41] give rise to dysfunctional skin-barrier in patients with AD, eventually leading to cytokine production, immune cell activation and inflammation.

Inside-out: The inside-out AD hypothesis suggests that keratinocyte barrier gets disrupted resulting in inflammation due to a deregulated immune system.[42] This hypothesis is supported by the fact that AD patients show up with genetic polymorphisms in chemokines, receptors and cytokines that include CCL5, CD14, IL-31, IL-22, IL-18, IL-13, IL-4).[43] Enhanced Staphylococcus aureus (SA) infection and AD risk are being conferred by genetic polymorphisms in Toll-like receptors (TLRs).[44] The antimicrobial peptides (AMPs) tend to decrease during atopy and are linked to colonization with SA, increased pH, fatty acid loss and increased TEWL.[45] In AD patients, there is an increase in the activity and number of a variety of CD1a+ and CD11c+ subsets of dendritic cells (DCs), specializing in presentation and uptake of antigens to lymphocytes, thereby contributing to T-cell polarization and activation.[46] AD patients also have increased activity of innate lymphoid cells (ILCs)-type 2 that produce IL-13 and IL-5 and activate DC.[47] Increased activation of type 2 inflammation, type 2 ILCs and DCs are preceded by an increase in thymic stromal lymphopoietin (TSLP) and keratinocyte-derived IL-33, IL-25, in atopic skin. Th2 cell activity dominates almost all AD stages, as evidenced by the increase in levels of chemokines and type 2 cytokines (CCL5, IL-31, IL-13, IL-10, IL-5 and IL-4),[48] leading to increase in skin permeability to external pathogens and antigens.[43,44] Th1 activity is upregulated in the late AD stages, giving rise to higher IFN-γ and resulting in keratinocyte apoptosis.[49] Th17 cells known for producing IL-22 and IL-17 show decreased activity but are increased in numbers in AD; however, their contribution toward AD pathogenesis remains elusive. AD patients also show increased activity and number of Th22 cells that produce higher IL-22 levels thereby inducing terminal keratinocyte differentiation and epidermal hyperplasia.[50]

Risk of ADHD in atopic dermatitis

In the early 1990s, studies to find the association between atopic diseases and ADHD were performed.[51,52] The hypothesis about the association of immune diseases with learning problems presented by Geschwind and Behan[53] encouraged them. There were conflicting findings in this regard; no statistical significance was found between asthma and ADHD association by Biederman et al.[52] or McGee et al.[51] while Roth et al.[54] indicated for the association between the two. A significant correlation was observed between atopy and ADHD as well as other behavioral disorders by Schmitt et al. in 2009[55] studied in a cross-sectional manner on adolescents and children with information between 2003 and 2004 from a German Health Care Database.

The association of AD with ADHD have now been shown by a number of studies. The very first work suggesting the link between AD patients and increased risk of ADHD was shown by a German cross-sectional study.[55] Significant linkage between AD and ADHD risk have also been established by large cross-sectional studies from United States,[21] Germany[56] and Taiwan.[57] An association between AD and ADHD was found by a German study on children's mental health problems involving 2916 infants when they observed early-onset AD in children significantly affects conduct problems that include hyperactivity/inattention.[58] Similarly, a Korean study provided evidence for the attention problem prevalent in AD treated children than in non-AD treated children.[59] AD and ADHD have also been found significantly associated in case control and longitudinal Taiwanese studies in ADHD diagnosed patients.[60,61] One of the studies found that patients with Tic disorder and ADHD have increased risk of presenting themselves with AD.[61] In 2014, Genuneit et al. studied a German birth cohort over a period of 12 years prospectively.[62] Using questionnaires from both treating physicians and parents, they found early-onset AD was significantly associated with early ADHD while late-onset AD was non-significantly associated with late ADHD. However, early AD was not found to be associated with late ADHD. Chen et al. performed a case-control study between (1997–2000) on patients born between 1997 and 2010 and found that atopic diseased children including those affected by AD have increased ADHD risk.[22] They

showed that the increased number of atopic diseases cause an increase in ADHD risk; however, they did not evaluate the risk of AD alone for the presentation of ADHD. Liao et al. studied a Taiwanese cohort between 2000 and 2010 involving the National Health Insurance Program and observed that AD infants of less than 2 years age have increased chances of developing ADHD.[63] Riis et al. hypothesized for the temporal nature of the AD and ADHD association while studying national registries, using medical prescription for ADHD or ADHD diagnoses in admission/outpatient.[64] As compared to the general population, they also found in AD patients, a substantial ADHD diagnoses risk.

AD and other neuropsychiatric conditions

AD patients seem to have greater chances of catching up with emotional problem, attention deficit/hyperactivity disorder, conduct problems/disorder, depression, anxiety and self-harm/suicidal ideation.[21,63,65] These risks are increased with severity of AD, additional allergic comorbidities, symptoms and persistence, apparent for both children and adults.[21,61,65,66] Temporality of the relationship between early AD and consequent risk for conduct disorder and emotional problems as well as ADHD have been established through longitudinal studies.[20,22] The reverse phenomenon also happens to be true-that is, childhood mental health/psychological problems tend to increase chances of AD development.[67] Although some of the studies have identified such associations to be AD specific,[20] others have found associations between other allergic comorbidities and AD.[65] In general, there appears to be a link between chronic childhood illnesses and mental health disorders.[67] AD's association with different mental disorder problems is by large independent of personal atopic disease history or familial history of AD, lifestyle and environmental risk factors.[20] Notwithstanding the role of genetic factors in these associations, it remains to be determined to what extent genetics exert its effects. Sleep disturbances[20,21] as well as decreased life quality and/or health anxiety[68] play a crucial role in the link between AD-associated mental health disorders. Allergic diseases have been found associated with psychotic experiences, learning delay, autism spectrum disorder, tic disorder and Tourette's syndrome. Autism spectrum disorder risk is increased by the severity and number of allergic diseases[21]; similarly, severity of autism spectrum disorder is increased by allergic symptom frequency. However, uniform reproducibility of these results has been questioned. The relationship between AD and autism spectrum disorder was found to be specific according to one study,[65] while others have found a specific linkage with asthma and/or non-existent to weak AD association.[69] Recent works have indicated for the linkage between AD and epilepsy and the increase in epilepsy risk depend on the number of allergic diseases along with allergic rhinitis and AD severity.[61] This effect is not observed in adults but in children that can perhaps be attributed to the lesser adult-onset epilepsy incidences. AD and epilepsy association, unlike asthma, does not appear to be dependent on environmental factors and neither on obesity.[61] The mechanism underlying the associations with psychiatric and neurologic conditions is only but poorly understood. Recently, systemic Th2 cytokine increase has been traced to central nervous system diseases, indicating early exposure to be the cause. The other contributors may be AD patients with increased head injury risk, dysregulation of hypothalamic-pituitary-adrenal axis owing to systemic corticosteroid exposure or early life chronic inflammation.[3,65] AD patients show increased sympathetic excitability (emotional excitability, higher anxiety, depression, lower vagal activity and higher heart rate).[70] AD patients have shown themselves with sympathetic overactivity and higher heart rate, even when without stress that lead to sleep disturbance, which in turn have been linked to neuropsychiatric disease presentation.[71] Although AD shows increase in cerebrovascular diseases, meningitis/encephalitis, concussion and head/brain injury, epilepsy risk is greater even after these disorders are adjusted.[61]

Proposed mechanisms underlying AD-ADHD association

Three possible mechanisms underlying the AD -ADHD association have been proposed by Buske-Kirschbaum et al.[18] They are as follows: (1) inflammatory cytokine release due to chronic disease-related increased emotional stress levels and/or heightened Th2 inflammatory pathways seem to intervene with developing neurotransmitter systems

and mature prefrontal cortex (PFC) regions, directly involved in the pathology of ADHD. Since, it is not possible to separately examine the individual aspects of this mechanism, it needs to be simplified by analyzing the effect of AD-related elevated stress and immunomodulation on brain development and maturation in its entirety. (2) ADHD patients suffering from increased levels of psychological stress prompts AD involving neuroimmunological processes. (3) Considering AD and ADHD as two distinct problems with similar risks such as prenatal stress, genetics, environmental exposures, elevating both AD and ADHD predisposition, thereby explaining their co-occurrence. It is noteworthy to mention that none of the mechanisms mentioned above can be mutually exclusive. However, it is only reasonable to primarily focus on the concept of the AD-ADHD association cause involving chronic pruritic disease-related stress levels and increased modulatory cytokine levels, based on the studies published following the works of Buske-Kirschbaum et al.[18] and Schmitt et al.[20] All these factors together may interrupt prefrontal cortex maturation and intervene with neurotransmitter systems thereby leading to ADHD.

Neuromodulation and increased cytokine release

AD patients have presented themselves with a number of well-characterized immune abnormalities. Some of the identified changes involve: (1) enhanced Th2-typical cytokine quantities, for example, interleukin (IL)-31, IL-13, IL-5, IL-4, as well as IL-33, IL-25, thymic stromal lymphopoietin and high mobility group box (HMGB) 1 protein.[72] (2) Increased Th2 cell numbers, in particular CD4+ cells and elevated high affinity IgE receptor expression on Langerhans, eosinophil and dendritic cells.[72] Th2 cells producing IL-13, IL-5 and Il-4 and epidermal dendritic cells dominate flare-ups and acute diseases while cellular infiltration with both Th1 and Th2 and to a lesser extent with Th22 and Th17 cells is demonstrated during chronic AD.[48] Th1 cells are known by the production of IL-2, tumor necrosis factor (TNF)-b, interferon (IFN)-γ, while the source of IL22 and IL17A are the Th22 and Th17 subsets respectively. Hallmark modifications during systemic immune-regulation include allergen sensitization, elevated levels of allergen-targeting IgE antibodies, as well as circulating T cell polarization by Th2.[2] Considering the increased level of local immune response, the acute AD phase seem to be Th2-mediated with enhanced intradermal and circulating typical Th2 cytokine levels such as IL-33, IL-31, IL-13, IL-5, IL-4 and thymic stromal lymphopoietin.[73] Other immune active cells relevant to AD are recruited and activated by Th1-related cytokines like IL-2, TNF-b and IFN-γ; these cells associate with the immune responsive cells implicated in AD. In AD, a number of serological changes are known that include increased total IgE serum concentration, macrophage-derived chemokine, activation and thymus-regulated chemokine, IL-31 and cutaneous T-cell attracting chemokine; all of these are implicated immunologically leading to AD severity.[74] The data indicate clearly that both chronic and acute AD affected individuals are exposed to augmented inflammatory cytokine levels. Interestingly, there are evidences to indicate that neuroimmunological pathways involving both emotionally and behaviorally related cognitive systems could be activated by these cytokines. Studies on animal models suggest that increased IgE levels and allergen-stimulated reactions result in limbic brain induction and subsequently impeded social behavior, anxiety or avoidance behavior.[75] Human studies using functional magnetic resonance have indicated alteration in PFC neuronal activity upon chronic allergic response. Any operational change in PFC regions is associated with all the characteristic features of ADHD such as cognitive disturbances like inexpedient motor output, disturbed decision-making and reduced attention control.[76] The exact effect of augmented inflammatory cytokines as observed in AD presentation on higher cognitive functions and PFC is not fully elucidated but it is only reasonable to believe that multiple mechanisms are involved. It could involve direct facilitation of specific cytokine transporters of the blood brain barrier or passage through blood brain barrier; indirectly it could involve novel neurotransmitter/cytokine production from the microglia or blood barrier associated endothelial cells.[77] Finally, there is also a possibility that the CNS structure and function gets indirectly affected through circulating cytokines by afferent fiber activation.[78] In addition, to these causes of effect, it has been found that key neurotransmitter metabolism gets altered by the action of inflammatory cytokines. Some of the

neurotransmitters include norepinephrine dopamine, which have been found to be critically involved in the pathophysiology of ADHD.[79] These changes, which were first observed in animal models showed comparable deviations that have also been described for ADHD patients later on; this is partly due to increase in glucocorticoid (GC) levels, since stress-induced increased GC levels lead to weakened flexibility of cognition that require functioning PFC.[80] Altogether, it can be surmised that the increased inflammatory cytokine levels in patients with AD may indirectly or directly affect ADHD-related brain parts such as the PFC regions. Emotional control and motor regulation and behavior may be disturbed by the alteration in the regulation of neurotransmitter systems-these events are regarded calamitous with early onset AD when the brain is vulnerable and immature.

Psychological stress

The AD patients and their family experience AD-related stress and toil and consequent reduction of life quality. Multiple negative impacts have been linked to the changed physical appearance and tormenting pruritus, for example, impaired social and cognitive performance, altered mood, sleep disturbance and psychological stress. Furthermore, feelings of hopelessness and aggravated stress levels are caused as a result of discrimination and stigmatization. A dysfunctional parent-child relationship that may cause lessened support and prompts anxiety can also be included among some of the other effects.[81] Both human and animal studies have demonstrated that the brain behaves very sensitively to childhood and infancy stress, owing to the significant degree of developmental changes that are associated at this stage of life. Again, in studies involving monkeys and rodents, GCs play a critical role. Here, it is found that obstructed feeding or maternal separation result in increased GC levels that in turn cause reduced PFC functions. Additionally, this also causes increase in the level of central GC-receptor density thereby inducing altered neurotransmitter pathways in the long-term.[82] Also, there is evidence for the ADHD-relevant neurotransmitter pathway changes with early life stress. Maltreated girls presented themselves with enhanced catecholamine levels that correlate positively with the mistreatment duration.[83] Pruessner et al. observed that under stressful conditions in poorly parented children, dopamine synthesis was increased, suggesting for an influence of dysfunctional child-parent relationship on normal brain development.[84] Altogether, there is literary evidence to suggest that chronic diseased condition-related problems can be a causative agent for AD and consequent presentation of ADHD. Elevated GC levels in AD children may intervene with both the development and maturation of brain parts related to ADHD, such as the hypothalamus-pituitary-adrenal axis and PFC. It is highly likely that altered structure and function of those brain regions results in cognitive impairment and subsequent ADHD.

Confounders of AD-ADHD association

Sleep disturbances

The strongest factor affecting the AD-ADHD association has been found to be sleep disturbance. An analysis of 6484 children in the Romanos et al. study found AD-ADHD association in those with concurrent disturbed sleep while no association could be observed in children without any problems in sleep.[56] Yaghmaie et al.[21] and Strom et al.[85] thoroughly evaluated the association between AD and the quality of sleep partially using the National Survey of Children's Health data. Eczema shared a strong relationship with ADHD, which was increased in children with 0–3 nights of enough sleep as compared to children with 4–7 nights of enough sleep each week.[85] In children without eczema, ADHD and inadequate sleep were found to be not strongly associated. ADHD in children suffering from severe eczema and having inadequate sleep was significantly increased as compared to children with adequate sleep and without eczema; however, the risk of developing ADHD in children with adequate sleep and severe AD was not to the same extent. These observations support the results of Yaghmaie et al. study of 2013.[21]

Other atopic diseases

Other atopic diseases as confounders of AD-ADHD association have been evaluated and it has been found that atopic diseases like allergic rhinitis, conjunctivitis and bronchial asthma pose as potential risk factors for ADHD development. These atopic diseases as co-contributors along with AD

show an increased chance of developing ADHD; however, not as strong as disturbed sleep. Taken together all the observations from these studies, it seems more likely that other atopic diseases coexisting with AD remarkably increase the risk of ADHD development.

Conclusion

ADHD is characterized by pervasive, persistent and impaired levels of impulsivity/hyperactivity and/or inattention. ADHD is regarded as a common neurodevelopmental disorder with a high prevalence rate around the world. ADHD is often found comorbid with conditions like sleep disturbances, specific learning disorders, conduct disorder, oppositional defiant disorder, substance use disorders, mood and anxiety disorders, somatic conditions like obesity as well as neurodevelopmental disorders like autism. ADHD is a heterogeneous and complex disorder while considering brain correlates, presented by an erratic interplay between different neuronal networks. The etiology of ADHD involves an interaction between environmental and genetic factors, the prevalent ones being low birth weight, prematurity, and maternal alcohol or smoking while pregnant.

AD on the other hand also presents itself with a high prevalence suggesting that the general practitioners and dermatologists encounter this disease quite frequently. Lies at the root of AD is a complex combination of an immune dysfunction and acquired inborn barrier. Recent studies have raised the possibility that this chronic dermal ailment may lead to an increased susceptibility toward psychiatric comorbidities, the most important among them being ADHD. The idea of extended period of psychoneuroimmunological and psychoendocrine effects from aggravated levels of inflammatory, increased stress, disturbed sleep, continuous sensory stimuli, behind the association of AD and ADHD is only but poorly elucidated. Data suggest that children suffering from AD show an increase of –1.5-fold for ADHD comorbidity.[20] This review outlines various factors affecting the association of childhood atopic dermatitis and attention deficit/hyperactivity disorder and argues for AD as one of the most prominent risk factors of ADHD. Altogether, this review highlights the need for future work studying the various mechanisms associated with such multimorbid childhood population and find out appropriate preventive measures. An effort for identifying psychotherapy, psychiatric comorbidities, as well as basic research leading to the discovery of newer drugs for relevant treatment altogether can result in the alleviation of the comorbidity of AD and ADHD.

Limitations

Much of the conclusion derived in this review on the association between AD and ADHD is limited to cross-sectional studies. ADHD and atopy in general show a positive association in majority of the cross-sectional studies. However, any conclusion drawn on the temporal nature of such association warrants caution in absence of prospective longitudinal data.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Ping Li https://orcid.org/0000-0003-4061-7788

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