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Low Plasma Levels of Contactin-Associated Protein-Like 2 in Children with Autism Spectrum Disorder: Links to Neural Development

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Background: Autism spectrum disorder (ASD) is a condition of atypical neurodevelopment and is characterized by social communication problems and repetitive patterns of behavior. Early diagnosis and intervention are decisive for managing symptoms and improving outcomes. Contactin-associated protein-like 2 (CNTNAP2) protein is implicated in neural development and plays a role in brain connectivity and synapse formation. Genetic research has shown a possible link between CNTNAP2 and ASD.

Aim: We aimed to discover the blood plasma levels of CNTNAP2 in children with ASD and explore the potential association between CNTNAP2 concentrations and ASD severity.

Methodology: This case-control study included children with ASD (n=40) and aged-matched healthy controls (n=40). Blood plasma levels of CNTNAP2 were measured using enzyme-linked immunosorbent assay (ELISA). The Children Autism Rating Scale (CARS) and Social Responsiveness Scale (SRS) were used to assess the severity of the ASD. Spearman correlation coefficient (r) was used to correlate the variables.

Results: Children with severe ASD had significantly lower CNTNAP2 levels (0.31 (0.14) ng/mL, p=0.003) compared to normal controls (0.47 (0.24) ng/mL). However, CNTNAP2 levels of children with mild autism (0.44(0.22), ng/mL, p=0.77) were not significantly different as compared to normal controls (0.47 (0.24) ng/mL). Furthermore, a significant difference was found between CNTNAP2 levels, by comparing the mild and severe groups based on the CARS (p= 0.05). Furthermore, no significant correlation between CNTNAP2 levels, and severity scores (CARS and SRS), was obtained. However, a significant correlation between CNTNAP2 and age was observed.

Conclusion: The low CNTNAP2 plasma level in children with ASD indicated that it might be involved in the pathophysiology of ASD. Nevertheless, these results should be interpreted with care till more studies are achieved using a larger population to decide whether the reduction in CNTNAP2 plasma level is a mere outcome of ASD or it plays a pathogenic role in the disease.

Keywords: autism spectrum disorder, contactin-associated protein-like 2, children autism rating scale, social responsiveness scale

Introduction

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder identified by impairments in language progress, social communication, and repetitive actions.[1] The etiology of ASD is very complicated and varied. A combination of environmental, immunological, and genetic features is supposed to eventually result to the ASD.[2]

Despite enormous research attempts over the previous years, the pathophysiology of ASD is not clear. A growing body of literature indicated that there is emerging evidence and developing apprehension that an atypical blood protein, behavioral and neurological abnormalities play an important role in the pathophysiology of ASD.[3]

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There are no precise clinical or biological markers have been identified so far for diagnosing ASD. However, the search is continuing to find specific diagnostic clinical biomarkers for ASD, as well as for ASD subtyping. Additionally, in search of prognostic biomarkers, numerous studies have investigated different proteins in the blood of ASD subjects.[4]

Contactin-associated protein-like 2 (CNTNAP2) is a cell adhesion protein of the neurexin family. It is mostly expressed in both frontal and temporal lobes of the developing human brain, the frontal cortex and striatal circuits of the adult brain.[5] Additionally, human brain expression studies show high abundance in different cortical parts during embryonic stage.[6] CNTNAP2 has been demonstrated to play a key role in the early growth of the central nervous system (CNS) and synaptic functions in multiple neurodevelopmental disorders, including ASD,[7–9] intellectual disability (ID), and specific language impairment (SLI),[10] epilepsy[11] and schizophrenia and depression.[12] However role of CNTNAP2 in the CNS is not fully understood.[13] Deficiency of CNTNAP2 in neurons results in decreased interneurons, cortical layer modeling, and modifications in neuronal migration. Moreover, it is investigated that suppression of CNTNAP2 expression in the prefrontal cortex results in the decrease of functional synapses number and disproportion of excitation and inhibition (E/I) balance.[14] However, the fundamental cellular mechanisms are still not clear. Furthermore, functional studies indicated that CNTNAP2 was implicated in neuron migration, connectivity of specific neural circuits, subsequent laminar organization, and dendrite stabilization.[15,16] Several studies also showed that CNTNAP2 may play various roles throughout post-natal growth of cortical neurons and support to normal neuronal assembly and activity.[17]

Autism spectrum disorder (ASD) is supposed to result from abnormal growth of neural network and synaptic activity. Recent study[14] shown that CNTNAP2 is essential for synaptic function and ASD like symptoms resulted by decreased excitatory synaptic transmission in pyramidal neurons of prefrontal cortex. Chiocchetti et al,[18] conducted a functional and genetic study of the CNTNAP2 protein in ASD but the molecular association between ASD and CNTNAP2 is unclear. Genetic, and imaging studies offer strong evidence for the CNTNAP2 gene as a risk factor for many neurodevelopmental disorders, including ASD.[19]

Anti-Contactin-associated protein-like 2 antibodies are linked with encephalitis (group of autoimmune diseases) causes substantial damage to the peripheral and/or central nervous system.[20] Coutinho et al,[21] reported that CNTNAP2 autoantibodies were elevated during pregnancy in mothers of babies born with psychological and mental disorders. CNTNAP2 knockout neurons presented decreased axonal development and synaptic irregularities, which might contribute in ASD.[22] Furthermore, deficiency of CNTNAP2 in mice indicated core symptoms of ASD including stereotypic as well as communication and social behaviors.[11,23]

Earlier studies also supported that CNTNAP2 was linked with ASD in the Brazilian,[24] Iranian,[25] and Korean[26] population. However, some other studies found no association between CNTNAP2 and ASD.[8,27] Recently George-Hyslop et al[7] reviewed the published studies on CNTNAP2, including expression, disease associations, and molecular/cellular mechanism. The complete loss of CNTNAP2 contributes to the pathogenesis of neurodevelopmental disorders through variable alterations in numerous features of human cerebral cortex excitatory neuron growth that result in irregular neural network development and function.[28] Moreover, a well-documented meta-analysis is necessary to discover the association between CNTNAP2 and ASD.

A number of independent studies have reported the importance of CNTNAP2 in the aetiology of both ASD and language impairment.[6,29] Moreover, many studies have identified the contribution of common variants of the CNTNAP2 gene polymorphism and ASD.[25,26,30] Fang Fang et al[30] reported the connection between childhood ASD and single nucleotide polymorphisms CNTNAP2 gene, in a Chinese population. Findings suggested that CNTNAP2 gene is linked with risk of childhood ASD and also associated with the severity of language impairment in children with ASD. It was recently reported that children with ASD have significantly low CNTNAP2 protein levels,[31] however further details are not available. Martı´n-de-Saavedra et al, analyzed[32] the CNTNAP2 as a cerebrospinal fluid (CSF) biomarker for ASD patients and suggested CNTNAP2 as a potential target for the treatment of epilepsy that is usually associated with ASD. Since CNTNAP2 plasma levels in ASD subjects have never been reported earlier, thus considering the crucial role of CNTNAP2 in the brain development and neurological function in CNS, and its association with ASD has led to the hypothesis that CNTNAP2, could play a key role in the pathophysiology of ASD and may act as useful biomarker. Therefore, we aimed to explore the blood plasma levels of CNTNAP2 in children with ASD and healthy controls and their association with the severity of ASD.

Materials and Methods

Participants

This case-control study was conducted at the Autism Research and Treatment Center (ARTC), at King Saud University (KSU) Riyadh, Saudi Arabia, from September 2023 to March 2024. Forty (40) subjects with ASD, aged between 2 and 12 years (M ± SD = 6.27 ± 2.10 years), from the ARTC at KSU, and the control group consisted of 40 age and sex-matched neurotypical children from the pediatric clinic at the King Saud medical city Riyadh, Saudi Arabia, were included in the present study. ASD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[1] Participants associated with fragile X syndrome, epileptic seizures, obsessive-compulsive disorder, affective disorders, or any additional psychiatric or neurological diseases were excluded from the study. The IBR Committee of the King Khalid Hospital at King Saud University in Riyadh, Saudi Arabia, approved the present study. Also, informed written consent was signed by the parents or the legal guardians of all the enrolled participants. All procedures followed the Helsinki Declaration for human investigations.

Childhood Autism Rating Scale (CARS)

The Childhood Autism Rating Scale is a validated test to interpret autistic behavior and has been used to measure Autism severity.[33] It rates children from one to four on a scale of fifteen different symptoms or dimensions (including activity level; object use; body use; imitation; verbal and non-verbal communication; emotional response; relation to other people; response to listening; nervousness or fear; reliability and intellectual response level; adaptation to changes; visual responses; responses to touch, smell, and taste; and general impressions). According to this scale, scores of ≥30 strongly indicate that autism is present. Children who score 30–36.5 are mild to moderately affected by autism and those with scores ranging from 37 to 60 points are severely affected by autism.[33]

Social Responsiveness Scale (SRS)

The Social Responsiveness Scale (SRS) is a validated test of interpersonal behavior, communication, and stereotypical traits in autism[34] It is used as a diagnostic tool, to distinguish clinically significant ASD from varying levels of social impairment in other psychiatric disorders. It consists of 5 subscales: (1) social awareness, (2) social cognition, (3) social communication, (4) social motivation, and (5) autistic mannerisms. Total SRS raw scores range from 0 to 195, corresponding to significant social impairment as observed in individuals with ASD. A score of 76 or higher is considered severe and is strongly associated with a clinical diagnosis of autistic disorder. A score between 60 and 75 is in the mild-to-moderate range of social impairment.[34]

Blood Sample Collection

Blood samples from the participants were drawn after overnight fasting. Blood was taken into 3 mL EDTA-containing tubes for blood collection. The samples were centrifuged directly after the blood sampling for 20 min at 4°C at 3000×g. Until analysis, the plasma was kept at −80°C. CNTNAP2 concentrations were measured in the plasma of autistic subjects using a commercially available sandwich ELISA kit (Cusabio Biotech Co. Ltd., Wuhan, China). All biochemical analyses were performed in duplicate, and mean values were reported. No significant cross-reactivity or interference was observed.

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences, version 21, software (SPSS Inc., Chicago, IL, USA). The normality of results was tested using the SPSS software program by the Kolmogorov–Smirnov test. For the non-parametric data, the Mann–Whitney test was used for comparison. For the normally distributed data, the independent-sample *t*-test was used to compare the means between the autistic group and the control group. The descriptive statistics [mean and standard deviation (M ± SD)] were used to describe the outcome. The correlation between different variables (CNTNAP2, Age, CARS, SRS) was determined using the Pearson correlation coefficient (r). For all tests, Statistical significance is defined as a p-value ≤0.05.

Table 1 General Characteristics, Plasma Levels of CNTNAP2, in Children with ASD and Healthy Controls and Their Association with ASD Severity

Groups	Number of Subjects/ (Sex)	Mean Age in Years (M ± SD)	CNTNAP2 ng/Ml (M ± SD)	*p*-value*	CARS Score
ASD (severe and mild-moderate)	40 (m=35; f=05)	6.27 (2.10)	0.38 (0.20)	0.06[§]	> 30
Severe ASD	19 (m=17; f=02)	6.41 (2.04)	0.31 (0.14)	0.003[$]	> 36.5
Mild to moderate ASD	21 (m=18; f=03)	6.38 (1.69)	0.44 (0.22)	0.77[#] 0.05[∞]	< 36.5
Healthy controls	40 (m=33; f=07)	6.95 (3.44)	0.47 (0.24)		

Notes: [§]Autism v/s controls; [$]Severe autism v/s controls; [#]Mild to moderate autism v/s controls; [∞]Mild to moderate autism v/s severe autism (*p-value= ≤ 0.05 was considered statistically significant).

Results

The general characteristics of the study participants and plasma levels of CNTNAP2 in autistic (n=40) and control children (n=40) are summarized in Table 1. CNTNAP2 (M ± SD) levels were compared between autistic children with different severity of autism (mild-moderate or severe) and age-matched healthy controls (Table 1). ASD subjects were classified according to their recorded CARS and SRS scores.

Results show that plasma CNTNAP2 (M ± SD) levels in children with severe ASD were significantly lower (0.31 (0.14) ng/mL, p=0.003) compared to normal controls (0.47 (0.24) ng/mL). However, CNTNAP2 levels of children with mild-moderate autism (0.44(0.22), ng/mL) were not significantly (p=0.77) changed as compared to normal controls (0.47 (0.24) ng/mL). Furthermore, a significant difference was also found between CNTNAP2 levels, by comparing the mild-to -moderate group to severe autism group based on CARS score (p= 0.05).

The severity of ASD in children was further classified according to their measured CARS and SRS scores. Based on the CARS scoring scale, twenty-one children (51%) had mild to moderate autism with (31.5± 2.24), and nineteen children (49%) had severe autism with (41.5 ± 2.70).

According to the SRS scoring scale, eight participants (20%) had mild to moderate impairment in social skills with mean (70.63± 3.25), and 32 subjects (80%) with severe impairment in social skills with (126.5 ± 53.1) scores, which are considered typical and strongly linked with a clinical diagnosis of ASD (Figure 1).

Additionally, Spearman correlation coefficient (r) was calculated to determine the relationships between CNTNAP2 levels and different variables (CARS, SRS, and age) as shown in Figures 2–4. The resulting graphs showed no significant correlations between CNTNAP2 levels, CARS (r = −0.0199, p= 0.217), and SRS (r = −0.144, p= 0.376) among ASD patients, suggesting CNTNAP2 may not be associated with disease severity or progression. However, a significant correlation between CNTNAP2 and age was observed (r=−0.339, p=0.032).

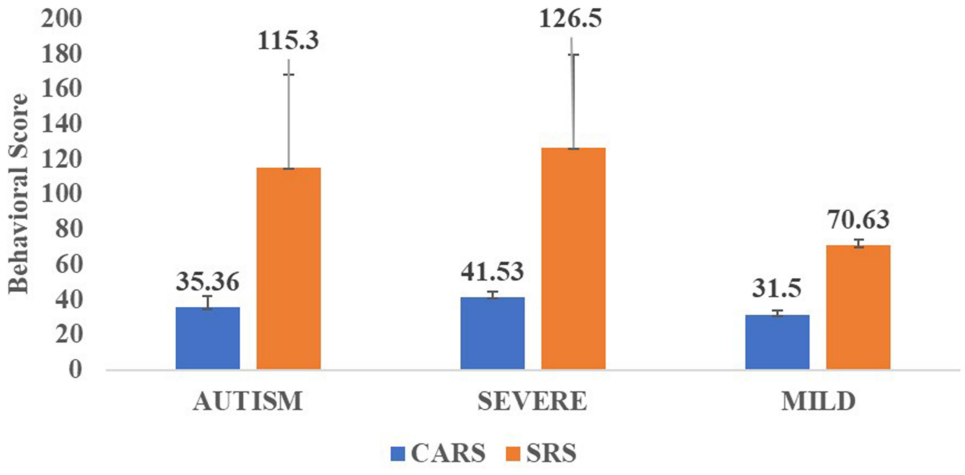

Figure 1 Behavioral scales (CARS, SRS) scores in children with ASD and their association with ASD severity.

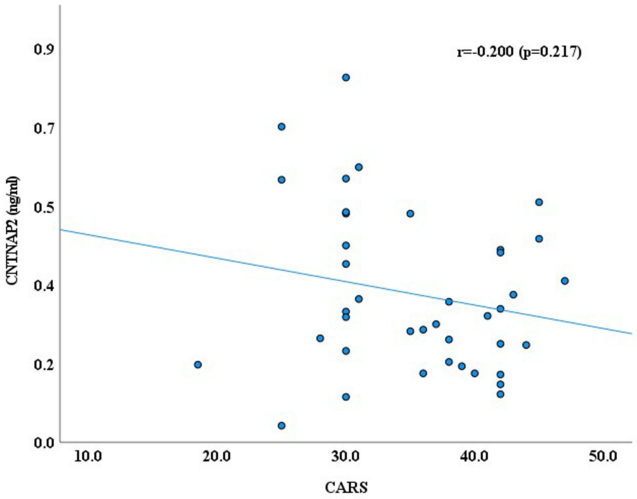

Figure 2 Correlation between the plasma levels of CNTNAP2 (ng/mL) and the CARS score in ASD children.

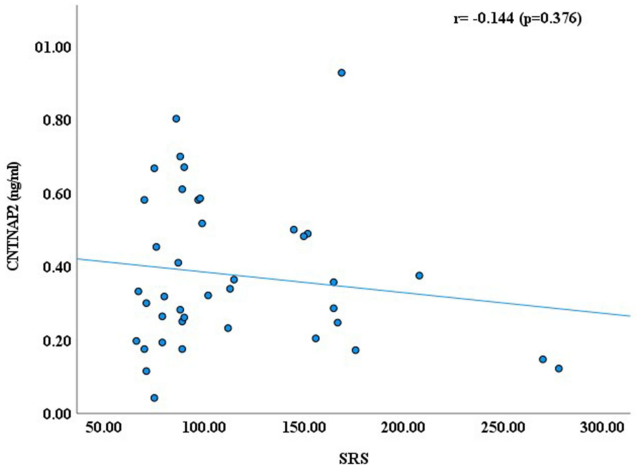

Figure 3 Correlation between the plasma levels of CNTNAP2 (ng/mL) and the SRS in ASD children.

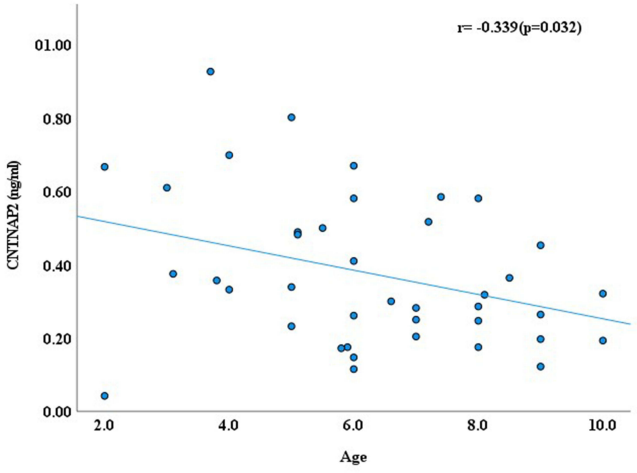

Figure 4 Correlation between the plasma levels of CNTNAP2 (ng/mL) and the Age in ASD children.

Discussion

The pathophysiology of ASD is not very clear, but it seems to implicate the dysfunction of many neurobiological systems. Biomarkers research in ASD has been usually limited to blood. Blood-based biomarkers are very important in the development of diagnostic techniques to classify disease or support as companion diagnostics to categorize patients most possibly to benefit from precise pharmacotherapies.[35] Search for potential biomarkers to identify the characteristics of ASD severity, like cognitive dysfunction and social defects, can provide us a better information on the ASD pathophysiology.[36]

Contactin-associated protein-like 2 (CASPR2) is a cell adhesion protein of the neurexin family that is mostly expressed in the neuronal membranes of the CNS and peripheral nervous system (PNS).[37] CNTNAP2 plays a central role in early brain development and neuronal differentiation including aberrant neuronal synchrony, reduction of GABAergic interneurons, and aberrant neuronal migration.[11,38] Furthermore, the major function of CNTNAP2 is to connect brain cells with each other at synapses and in the clustering of Potassium (K+) channels.[37,39]

Previous research studies have pinpointed the importance of synapse formation and stabilization, synaptic alteration, and functional connection formation processes in the etiology of ASD.[40] Irregularities in synaptic proteins like CNTNAP2 implicated in cell adhesion, signaling, or scaffolding, may determine the etiology of ASD.[41] Moreover, in humans, variants in genes encoding neurexins or neuroligins have been linked with ASD.[42] Practically, CNTNAP2 is implicated in the neuronal migration, neuronal network activity, and development of synaptic spines.[43] Additionally, CNTNAP2 knockout neurons showed reduced axonal growth and synaptic irregularities, which might play key roles in ASD.[22]

Former studies demonstrated sufficient evidence for the association of CNTNAP2 with genetic risk for ASD and particular brain structures,[7,24,26,30,] however, other studies reported no connection between CNTNAP2 and ASD.[8,9,27]

Given the conflicting results of the prior reported studies, we examined the CNTNAP2 plasma levels and the association of CNTNAP2 with Age, CARS, and SRS severity scores among children with ASD. The results offer significant evidence for the involvement of CNTNAP2, in ASD, but demonstrate no connection between CARS and SRS, however, age is significantly correlated with CNTNAP2 level. The cellular mechanisms underlying the dysfunction of CNTNAP2 and ASD are not known.

To our knowledge, this is the first study to reveal a significant decrease in CNTNAP2 plasma levels in children with ASD compared to healthy controls. The current study results showed that the plasma level of CNTNAP2 was significantly, lower in the ASD group compared to the control group. However, the levels of CNTNAP2 were not statically correlated to the degree of ASD (CARS and SRS). However, to obtain a decisive conclusion, more detailed studies with larger sample sizes are needed to confirm the results.

These results could have important suggestions for the diagnosis and therapy of ASD. They may also offer significant insights for neurodevelopmental disorders more generally, including those not directly involving CNTNAP2, but that may be contributed by similar pathophysiological mechanisms. Results also support that a reduced CNTNAP2 expression in the brain increases liability for ASD.[11,18,44,45] St George-Hyslop et al,[28] revealed that complete loss of CNTNAP2 contributes to the pathogenesis of neurodevelopmental disorders through complex changes in several features of human cerebral cortex excitatory neuron growth that culminate in aberrant neural network formation and function.

However, we could not find any data in the literature regarding the levels of CNTNAP2 protein in a single group of autistic children to compare our results. However, our findings support the previous reports of decreased CNTNAP2 gene expression in ASD.[11,44,45] Although caution should be exercised in the interpretation of our data, suggesting a potential role for CNTNAP2 in ASD.

The preliminary results reported in this study appear encouraging; and on the basis of the initial results, there seems to be suggestive evidence in support of CNTNAP2 contributions to the pathophysiology of ASD. Further studies on a larger population are required to confirm the relevance of the CNTNAP2 and to determine diagnostic accuracy to identify ASD patients at risk of a fast progression of disease.

Given the critical role of CNTNAP2 in human cerebral cortex evolution in neurodevelopmental diseases[7] we may conclude that lower plasma concentrations of CNTNAP2 may contribute to the impaired neuronal development and synapse formation in the brain of ASD.[7] The underlying biology is complex, as with many CNTNAP2 roles, based on the

biological setting. Therefore, mechanisms other than conventional pathogenic pathways are likely to be implicated in the biology underlying the CNTNAP2 association. This study provides evidence that higher CNTNAP2 may also provide protection in normal controls as compared to ASD subjects. It also supports the link between low CNTNAP2 levels in ASD to a potential association with neurodevelopmental changes.

Limitations

The first limitation of this study is the small sample size and its cross-sectional design. Second, adaptive behavior was not assessed in the control individuals. Therefore, whether levels of CNTNAP2 level may be related to behavioral features in healthy individuals remains to be confirmed. Third, all our participants were children, and we did not include any adolescents or adults. These results should not be generalized unless validated in older individuals.

Our results provide preliminary, direct evidence of altered CNTNAP2 levels in subjects with ASD, which may contribute to the early pathogenesis of ASD, offer valuable biomarkers, and point to novel therapeutic interventions. Further studies with larger sample sizes are required to elucidate the underlying biological mechanisms.

Conclusion

CNTNAP2 levels were found to be significantly lower in children with severe ASD compared to a control group and they were also not significantly associated with the Age, CARS, and SRS of subjects. Our findings suggested that CNTNAP2 may play a role in the brain development and synaptic functions in ASD and might serve as candidate proteins for future research into the molecular mechanisms of ASD or the discovery of ASD biomarkers. In addition, CNTNAP2 changes in peripheral blood may have therapeutic and/or diagnostic value. Further studies with larger samples are highly recommended to investigate the role of CNTNAP2 in ASD and to explain the mechanism behind it. However, these data should be treated with caution until further investigations are performed, with a larger subject population, to determine whether the decrease of CNTNAP2 levels is a mere consequence of ASD or has a pathogenic role in the disease.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The current study conforms to the Helsinki Declaration and was approved by the Ethics Review Board of the College of Medicine, King Saud University, Riyadh, Saudi Arabia (no: 23/0804/IRB).

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Disclosure

The authors declare that they have no competing interests.

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