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Cognitive function and retinal biomarkers as novel approach to diagnosing and assessing autism spectrum disorder

Sarah Al-Mazidi[1]✉, Abdulrahman Alhowikan[2,3], Nadra Elamin[3], Amani Abualnaja[4], Ahmad Al-Mnaizel[5], Turki Alharbi[6] & Laila Al-Ayadhi[2,3]

The retina is invariably considered an extension of the central nervous system and can predict cognitive impairment in neurodevelopmental and neurodegenerative disorders. This is due to the physiological and embryological link between the retina and the brain. Since this correlation was not previously tested in autism spectrum disorder (ASD), we aim to provide evidence for a correlation between retinal dysfunction and cognitive impairment in ASD children through previously reported retina and cognitive dysfunction biomarkers. 80 children were recruited to test biomarkers of the retinal function, Ciliary neurotrophic factor (CNTF), and cognitive function A Disintegrin and Metalloproteases 10 (ADAM10). These biomarkers were correlated with the Childhood Autism Rating Score (CARS) to distinguish ASD from cognitive impairment disorders and the Short Sensory Profile (SSP) as a sensory impairment indicator, including vision. ADAM10 was significantly decreased in ASD children compared to neurotypical children ($p < 0.01$). It also decreased as the severity of autism increased, as measured by CARS. We also found that CNTF decreases in ASD children with moderate severity compared to neurotypical and severe ASD groups, indicating that CNTF can be an early indicator of ASD. ADAM10 was directly related to CNTF, implying the direct correlation between the eye and cognitive function in ASD. ADAM10 is a potential indicator of cognitive function in ASD, and CNTF can be an indicator of retina function. The relationship between both biomarkers might serve as early diagnosis biomarkers and a potential therapeutic target in ASD.

Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders characterized by impaired social interactions and repetitive stereotypical behaviors[1]. Being one of the most common neurodevelopmental disorders, ASD has been linked to many pathologies, including neuroinflammation and brain development abnormalities[2,3]. Patients with ASD mainly show behavioral and cognitive symptoms commonly associated with systemic dysfunctions, including the immune, gastrointestinal, and neural systems. Many biomarkers have been linked to the severity of cognitive impairment that might serve as diagnostic and therapeutic targets for ASD patients with cognitive impairment[4]. Recently, abnormalities in the eye have been linked to mental and psychological disorders such as Alzheimer's disease. In addition, children with visual abnormalities show psychosocial and emotional behavioral impairment that resembles autistic traits[5]. These abnormalities observed in ASD patients are mainly in the retina, including changes in the macula, fovea, and membrane thickness[6]. Growing evidence indicates the relationship between the eye and autism, which can be a potential non-invasive diagnostic tool at an early age. In addition, new evidence of biomarkers of eye tracking was found to aid in diagnosing autism[7].

Early diagnosis and intervention of ASD have the best therapeutic outcomes for ASD children and improve their quality of life[8]. The diagnosis of ASD depends on behavioral and educational evaluation protocols testing the cognitive ability of ASD patients[9]. Accumulating evidence supports the association between different biomarkers in the pathophysiology of ASD[10]. Finding a diagnostic and prognostic biomarker for ASD would provide new

[1]Department of Anatomy and Physiology, Faculty of Medicine, College of Medicine, Imam Mohammed Ibn Saud Islamic University, P.O. Box: 5701, 11432 Riyadh, Saudi Arabia. [2]Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia. [3]Autism Research and Treatment Center, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia. [4]Internal Medicine, King Faisal Specialized Hospital and Research Center, Riyadh, Saudi Arabia. [5]John Hopkins Aramco Health care, Dammam, Saudi Arabia. [6]Orthopedics Department, Prince Sultan Military Medical City, Riyadh, Saudi Arabia. ✉email: s.almazeedi@gmail.com

insights into its pathogenesis, diagnosis, and, consequently, intervention. The most studied biomarkers of eye dysfunction and cognitive impairment were Ciliary neurotrophic factor and ADAM10.

Ciliary neurotrophic factor (CNTF) is a potent neurotrophic factor that stimulates and maintains neural survival and function[11]. It is one of the most well-known neurotrophic factors associated with retinal degeneration diseases. Many studies on animals showed neural restoration after CNTF injection. A study showed that blind animals showed behavioral and visual improvement after a single dose of CNTF[12]. CNTF improved vascularization and macula thickness, which was also abnormal in ASD[13,14]. Interestingly, CNTF given during early brain development ameliorated autistic behavior in an autistic rat model[15]. According to all the evidence mentioned above, increased CNTF levels may act as a neuroprotector in children with ASD and ameliorate sensory impairments, including vision.

Many biomarkers have been discovered for cognitive function. One of these biomarkers is A Disintegrin and Metalloproteases 10 (ADAM10). The ADAM10 is a member of type 1 transmembrane proteases, characterized by cleaving membrane-bound proteins of their extracellular domain[16,17]. It is highly expressed in the brain, mainly at the synapse, and functions as a sheddase of synaptic proteins[18]. Physiologically, ADAM10 regulates axon guidance, the immune system, and synaptic functions by cleaving synaptic proteins such as Amyloid-beta precursor *protein* (APP), neuroligins, and neurotoxins. The cleavage of APP induces synaptic dysfunction and the development of autistic-like behaviors in mice[16]. A recent study reported that decreased levels and activity of ADAM10 have led to abnormalities of innate immune response in microglial cells and caused social behavior deficits and repetitive behaviors in mice[17]. It is suggested that the changes in the ADAM10 levels are associated with early cognitive impairment in older adults[19,20]. The circulating ADAM10 and its substrate are potential diagnostic and prognostic biomarkers for cognitive impairment in Alzheimer's disease patients, and it is associated with mild cognitive impairment as an early indicator of cognitive dysfunction[20,21]. These findings were further supported by early treatment of ADAM10, which would rescue early stages of cognitive dysfunction[22].

As conventional ASD assessment heavily relies on subjective criteria that lack objectivity, a biomarker is a quantifiable sign of a biological condition that can be used to assess the development of the disease. This proposed study is critical for early ASD assessment.

Given the link between the retina and cognitive dysfunction, we aim to investigate this relationship by measuring well-known biomarkers of retina dysfunction measured by CNTF and cognitive dysfunction measured by ADAM10. We also aim to compare the levels of the biomarkers to the severity of ASD behaviors compared to age-matched neurotypical children and to evaluate its association with cognitive function.

Methods

This study was conducted at the Autism Research and Treatment Center, Faculty of Medicine, King Saud University and King Khalid University Hospital. Institutional Review Board and Guidelines of Health Sciences Colleges Research on Human Subjects, King Saud University, College of Medicine approved this study with relevant guidelines in accordance with the Declaration of Helsinki (Ref. No. 22/0122/IRB). Informed consent was obtained from all participants' parents or legal guardians before they participated in approving the processing and publishing of data. ASD diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Participants

Eighty children participated in this study (40 with ASD and 40 healthy children). Male children with ASD aged 3–12 years who fulfilled the inclusion criteria were recruited from the Autism Research and Treatment Center, Faculty of Medicine, King Saud University. The neurotypical group included 40 age-matched healthy male children who attended the King Khalid University Hospital pediatric clinic for routine follow-up. Participants with infectious diseases or neuropsychiatric disorders were excluded from this study.

Behavioral assessment

Childhood autism rating score (CARS)

This scale is used to measure the severity of autism and to differentiate ASD from children with cognitive disabilities[23,24]. CARS is a behavior rating scale that helps clinicians differentiate children with autism from those with other developmental disorders. The scale consists of 15 items, each addressing a specific characteristic commonly associated with autism. These characteristics include Relating to People. The cut-off score to distinguish ASD from non-ASD was 25.5, with good sensitivity and specificity. It helps to identify children with autism and determine symptom severity through quantifiable ratings based on direct observation. The CARS assesses children on a scale of 1 (normal) to 4 (severe abnormality), with higher scores associated with a higher level of impairment. The domains included the following: items relating to people, emotional response, imitation, body use, object use, listening response, fear or nervousness, verbal communication, nonverbal communication, activity level, level and consistency of intellectual response, adaptation to change, visual response, taste, smell, touch response, and general impressions. The total scores ranged from 15 to 60, with scores below 30 indicating a non-autistic range, scores between 30 and 36.5, mild to moderate autism, and 37 to 60 points, respectively.

Short sensory profile (SSP)

The short sensory profile (SSP) is a 38-item questionnaire used to rate a variety of sensory impairments, including visual sensation[25]. The caregivers completed the tasks. Each item on the SSP is measured on a 5-point Likert scale (1 being "Always" and five being "Never"). The questionnaire has seven subscales in the following areas: tactile sensitivity (seven items), taste/smell sensitivity (four items), movement sensitivity (three items), sensation

seeking (seven items), auditory filtering (six items), low-energy levels (six items), and visual/auditory sensitivity (five items). Lower scores indicate a more significant association with ASD. Scores range from a minimum of 38 to 190, with lower scores reflecting more significant levels of sensory behavior. The overall sensory response was categorized as follows: <142, severe performance (most significant frequency of sensory symptoms); scores between 142 and 152, mild to moderate; and scores between 153 and 190, no symptoms.

Items related to visual sensitivity include eye adaptation to light, tracking moving objects, including moving people and covering the eyes to protect them.

Measurement of plasma CNTF and ADAM10

Five milliliters of blood were collected in EDTA tubes from each participant in both groups. Samples were centrifuged to isolate the plasma, which was aliquoted and stored at − 80 °C until analysis. Plasma concentrations of CNTF and ADAM10 were measured by ELISA using a commercial kit, according to the manufacturer's instructions (human CNTF/ADAM10 ELISA kit, Wuhan EIAab Science Company, Wuhan, China). Samples and standards were added to the precoated plate with antibodies specific for CNTF and ADAM10 and then analyzed in duplicate for each protein of interest.

Statistical analysis

Data are presented as the mean ± standard deviation. Data were statistically analyzed using one-way repeated-measures ANOVA when comparing three groups: neurotypical, mild, moderate, and severe ASD. The Bonferroni correction was used to compare the levels of CNTF/ADAM10 in the normal and subcategories of CARS and SSP (mild–moderate, severe). Not normally distributed data (Shapiro-Wilk normality test) are presented as medians. Statistical analysis was performed with ANOVA and Dunnett's post hoc test to compare CNTF/ADAM10 levels in all subgroups. The Student's t-test was also used to compare the plasma levels of CNTF /ADAM10 in the ASD and neurotypical groups. The Mann-Whitney U test was used for data that were not normally distributed. A linear regression analysis determined the relationship between plasma levels of CNTF and ADAM10. Statistical analysis was performed using the SPSS software, version 25. Two-tailed tests for statistical significance were performed where $p < 0.05$ was considered significant. Statistical significance was denoted by $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

Results

Demographic

Table 1 presents the participants' characteristics. All the participants were males. The mean age of the ASD group was 6.3 ± 2.6, and that of the neurotypical group was 5.6 ± 2.4. Participants with ASD were categorized into mild, moderate, and severe categories according to the severity of the disease, cognitive level measured by CARS, and sensory impairment, including visual impairment measured by SSP.

Plasma levels of ADAM10 and CNTF in ASD and neurotypical groups

Table 1 shows the plasma levels of ADAM10 and CNTF in ASD and neurotypical groups. A significant decrease in ADAM10 was found in ASD children compared to neurotypical children ($p < 0.01$). ADAM10 decreased by more than 50% in ASD children compared to neurotypical children, while CNTF decreased by 26.2% in the ASD group compared with that in the neurotypical group (Fig. 1).

Comparing levels of CNTF and ADAM10 in ASD subgroups according to CARS and SSP

The ASD group was subdivided according to CARS as an ASD severity indicator into mild-moderate and severe ASD subgroups and according to SSP as an indicator of sensory impairment, including vision to typical and atypical (moderate and severe) ASD subgroups.

Then, plasma levels of CNTF and ADAM10 were correlated with CARS and SSP to determine the association between these biomarkers of cognition and the eye to the severity of the disorder and sensory impairment in children with ASD.

A significant change was observed between the plasma levels of CNTF and SSP scores. Results significantly ($p < 0.05$) showed that children with ASD with a typical sensory profile (391.1 ± 225) had higher CNTF levels than children with ASD with an abnormal sensory profile (229.8 ± 185) (Fig. 2). The mean plasma level of CNTF was higher in the mild to moderate ASD group (330.1 ± 222) than in the severe ASD group (275.9 ± 225), but this correlation was not significant.

The mild-moderate ASD group had a plasma level of ADAM10 of 7.2 ± 3.4 pg/ml, and the severe ASD group had a plasma level of 5.5 ± 1.9 pg/ml (Table 2). The two subgroups exhibited significantly lower plasma levels of ADAM10 than the neurotypical group ($p < 0.001$). These results indicated that plasma levels of ADAM10 decreased with the severity of ASD compared to the neurotypical group (5.9 ± 2.5 pg/ml) (Fig. 3).

Characteristic	Control (mean ± SD)	ASD (mean ± SD)
Age (years)	5.69 ± 2.4	6.35 ± 2.6
ADAM10 (pg/ml)	11.01 ± 3.43	5.99 ± 2.49
CNTF (pg/ml)	390.6 ± 26	309.8 ± 22

Table 1. Demographics:

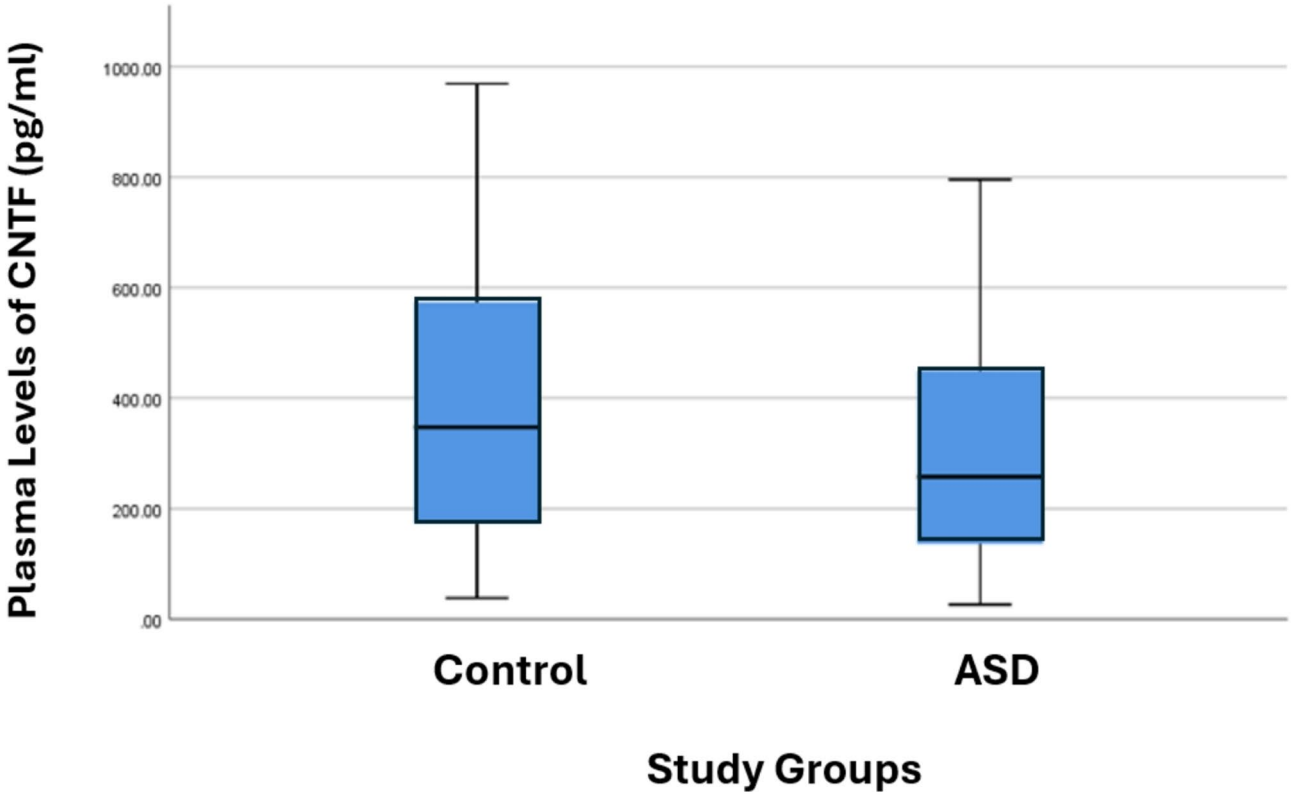


Fig. 1. Correlation between plasma levels of CNTF in ASD and neurotypical groups. There was a decreased plasma level of CNTF in ASD children compared to neurotypical children.

Relationship between ADAM10 as a cognitive function biomarker and CNTF as a retina biomarker in ASD children and neurotypical children

Linear regression analysis showed an interesting finding between cognitive impairment and retina dysfunction biomarkers. This relationship was positively correlated with neurotypical children but negatively correlated with ASD children (Fig. 4A and B).

Discussion

This study demonstrated for the first time a significant decrease in the level of ADAM10 in ASD children compared to neurotypical children, and this decrease in ADAM10 also corresponded to the severity of ASD and possibly cognitive impairment. ADAM10 is a synaptic protein that underlies synaptic plasticity and integrity and contributes to learning and memory processes. The dysregulation of the activity of ADAM10 is correlated with synaptopathy and brain function in neurodevelopmental and neurodegenerative disorders[26]. As previous studies reported the implication of downregulation of ADAM10 during neurogenesis in ASD, we suggest that ADAM10 may be implicated in the early stage of the disorder and can be an early indicator of ASD[27]. It has been widely accepted that synaptic dysfunction is associated with the development of ASD and cognitive impairment. It is also possible that the failure to process the synaptic adhesion molecules due to the decreased level of ADAM10 is responsible for the impairment of synaptic plasticity in ASD children[28,29]. Considering ADAM10's crucial role in brain development and its association with synapse, memory, and learning and the significant findings in our study, ADAM10 may play a vital role in the etiology of signaling, contributing to the cognitive and developmental defects observed in ASD.

The present study also showed a correlation between plasma CNTF levels and sensory impairment in children with ASD. The plasma level of CNTF was affected by the severity of ASD, and it was significantly higher in ASD children with typical sensory performance compared to ASD children with impaired sensory performance. In addition, CNTF levels are lower in children with ASD than in healthy children. These findings suggest that lower levels of CNTF in patients with ASD may affect the severity of sensory impairment. CNTF exerts its neuroprotective effects through the signal transducer and activator of the transcription-three-signaling (STAT3) pathway[30]. Astrocytes and Schwann cells express CNTF, which acts directly on neurons. When CNTF is available in the early stages of neuronal injury, it supports 60% neuronal survival. This supports our findings, where we also observed that CNTF levels in the mild-to-moderate severity subgroup were much lower compared to the severe ASD group. This might be because CNTF increases in the acute stages of neural dysfunction but normalizes in the chronic stages[31]. In addition, CNTF is primarily secreted as a neuroprotective factor in mildly or recently injured neurons; however, less CNTF has been observed in chronically injured neurons, which supports our findings[31,32]. The neuroprotective effect of CNTF has also been reported in neurodegenerative diseases such

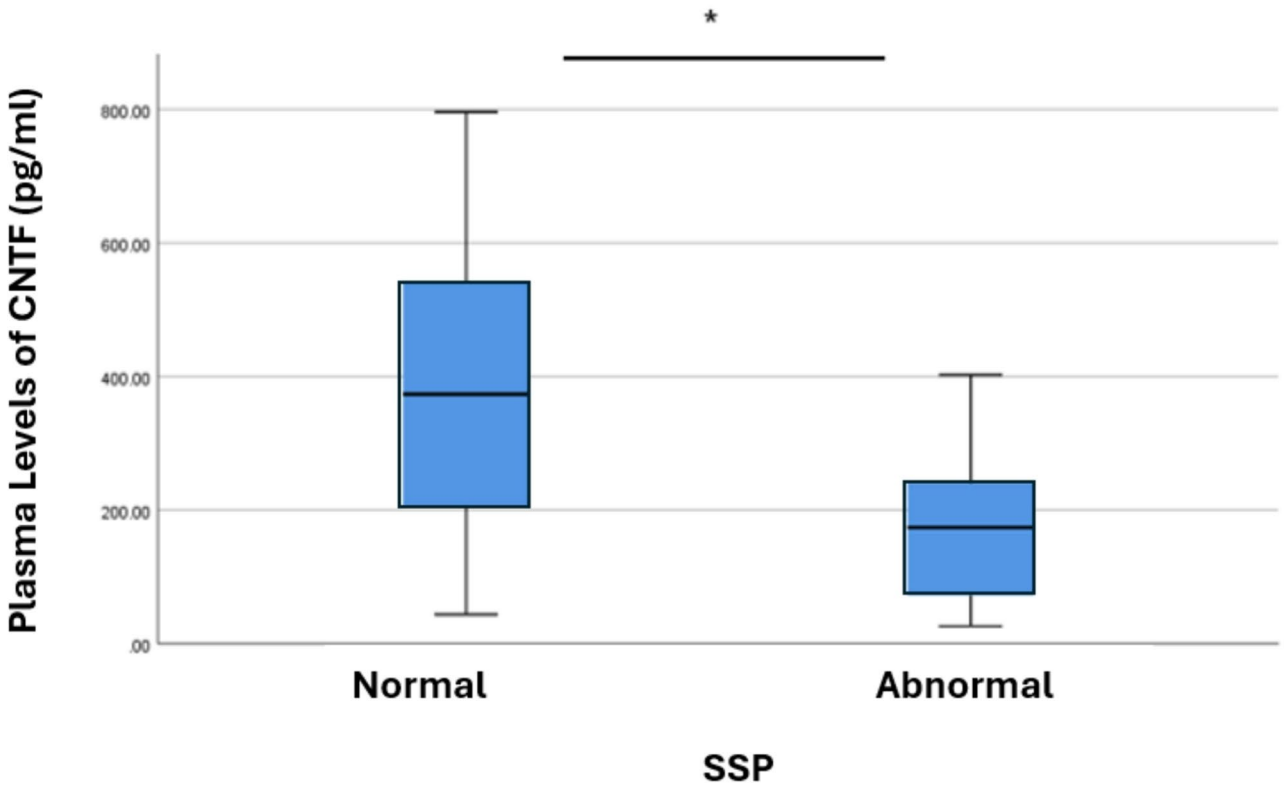


Fig. 2. Correlation between plasma levels of CNTF with the severity of ASD disease and the sensory profile (SSP). A significant decrease in plasma levels of CNTF in ASD children with atypical sensory performance in SSP ($p < 0.05$).

Test	ADAM10 (pg/ml)	CNTF (pg/ml)	*P* Value
CARS Mild to moderate ($n=19$) Severe ($n=21$)	7.17 ± 3.47 5.59 ± 1.95	31.2 ± 1.2 42.4 ± 6.4	$p<0.001$ for ADAM10
SSP Mild to moderate ($n=21$) Severe ($n=19$)	5.7 ± 2.22 6.59 ± 2.98	146 ± 3 113.6 ± 10	< 0.05 for CNTF

Table 2. Plasma levels of ADAM10 and CNTF in ASD according to the severity: SSP = Short Sensory Profile, CARS = Childhood Autism Rating Score, CNTF = Ciliary neurotrophic factor.

as Parkinson's disease[33]. Our results also showed that CNTF was decreased in children with ASD compared to healthy children, which agrees with a previous study that reported decreased CNTF levels in children with ASD. This study used sera from children with ASD to induce an ASD rat model; then these rat models were treated with a CNTF analog. These rats showed reduced behavioral signs of autism, suggesting that CNTF protects against neurotropic imbalance during early brain development[15].

The relationship between ADAM10 and CNTF has not been investigated. In our study, an interesting finding was the direct relationship between ADAM10 and CNTF, indicating a correlation between cognitive function and the retina in ASD. Also, CNTF was significantly decreased in children with ASD with impaired sensory performance. The sensory profile includes visual screening, previously correlated with CNTF. This sensory dysfunction in ASD might suggest retinal dysfunction. A previous study reported that photoreceptor waves in children with ASD were low, and treating the retina with CNTF protected the photoreceptors and improved their survival[34,35].

Many studies confirmed that CNTF prevents and reverses vision loss. A phase two study suggested that CNTF delivery to the eye improves vision in a dose-dependent manner and slows the progression of visual loss[36]. A phase one trial also showed that CNTF implantation in the retina enhanced visual acuity in patients with retinal neurodegeneration[37]. Neurological disorders have been associated with retina and retinal membrane changes. The newest discovery is that simple fundus imaging and optical coherence tomography can detect cognitive impairment. The disorders that were studied and found mounting evidence of the association between the retina and cognitive impairment severity are Alzheimer's Disease and Parkinson's disease. Since the retina is an extension of the central nervous system, it is logical that cognitive impairment can be detected through the

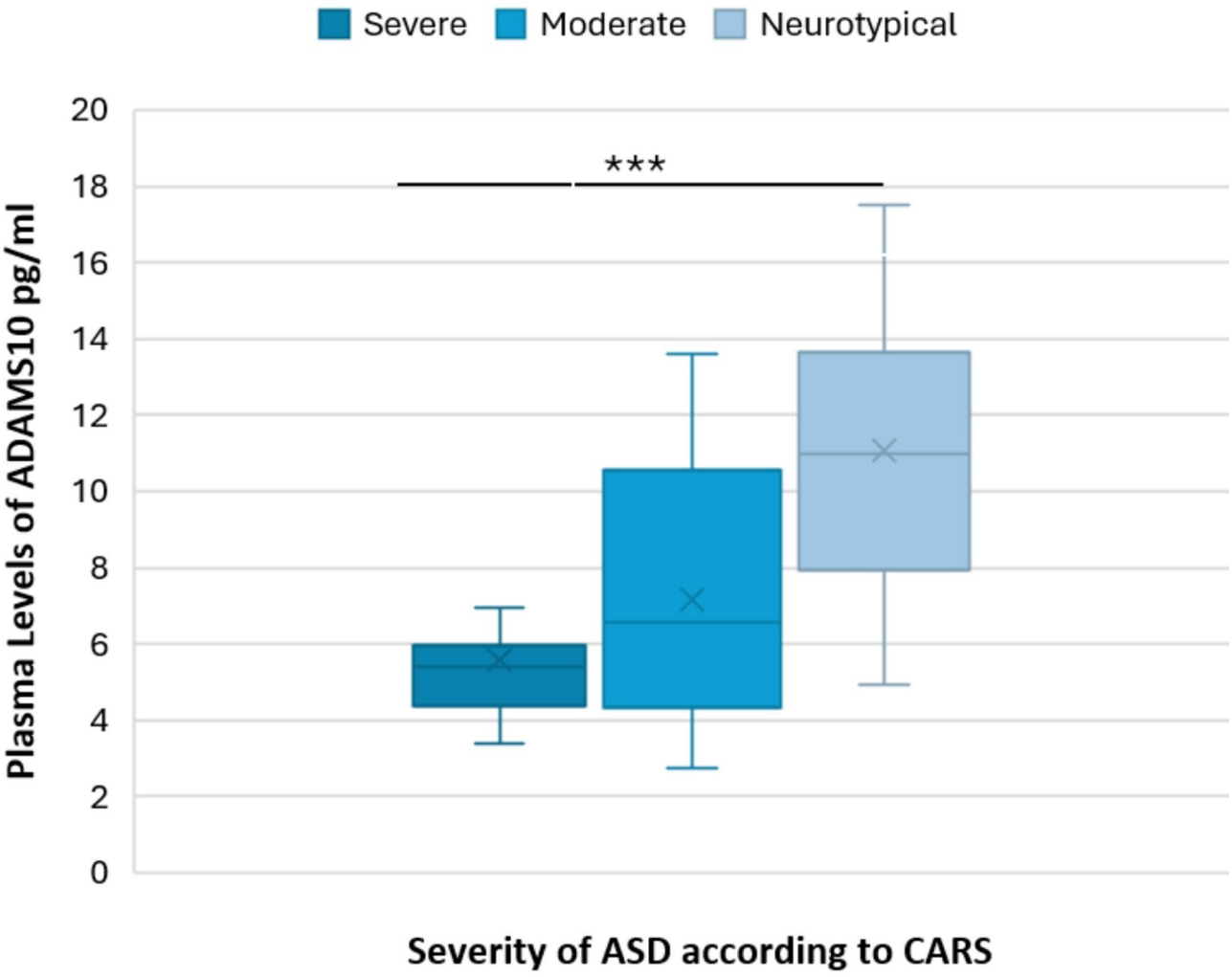


Fig. 3. Correlation between mean plasma level of ADAM10 (pg/ml) in neurotypical, Moderate, and severe ASD children. Plasma levels of ADAM10 significantly decreased as the severity of autism increased ($p < 0.001$).

retina. ADAM10, a biomarker of cognitive function, was also linked to the retina and is crucial for the normal development of the retina[38]. Also, in ADAM10 mono-transgenic mice, CNTF was a significantly regulated gene in cell communication and central nervous system development, supporting our findings regarding the direct relationship between these two biomarkers[39]. This relationship between cognitive dysfunction and the retina is demonstrated in our study, which showed a positive relationship in the biomarkers in neurotypical children but a negative relationship in the ASD group, indicating the importance of this relationship in ASD.

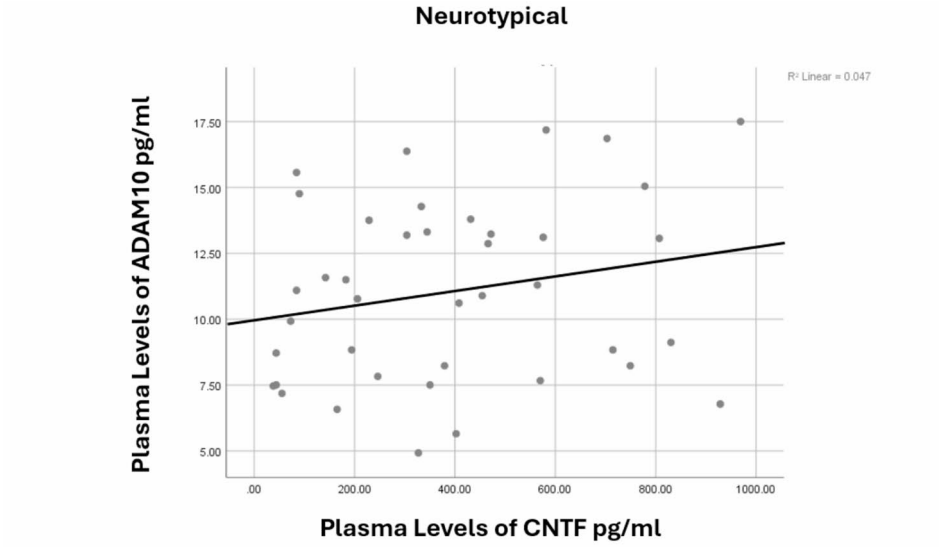
We suggest further investigation of this relationship, which shows a promising biomarker for early diagnosis, a prognosis indicator, and a possible therapeutic target. We also recommend testing this relationship in an autistic animal model to confirm the effectiveness of ADAM10 and CNTF biomarkers as therapeutic targets for ASD.

Limitations

One limitation of our study was the small sample size. Another potential limitation is the lack of previous research on plasma ADAM10 in ASD. Additionally, due to the nature of the study, we cannot detect the cause-and-effect relationship between the biomarkers in ASD pathology.

Conclusion

ADAM10 is a possible novel biomarker measuring cognitive impairment in ASD patients. Also, CNTF contributed significantly to sensory impairment, including vision. Both biomarkers might serve as new potential biomarkers associated with ASD as indicators of its severity. In our study, decreased CNTF and ADAM10 levels suggest a relationship between the eye and cognitive function in ASD, indicating their involvement during an early stage of the pathophysiology of ASD, which might contribute directly or indirectly to synaptic dysfunction in ASD. Therefore, there is a great need to identify the preferential substrates of ADAM10 involved in the different stages of ASD. Additional studies on the functional role of ADAM10 in ASD may provide a therapeutic target for ASD.



(A)

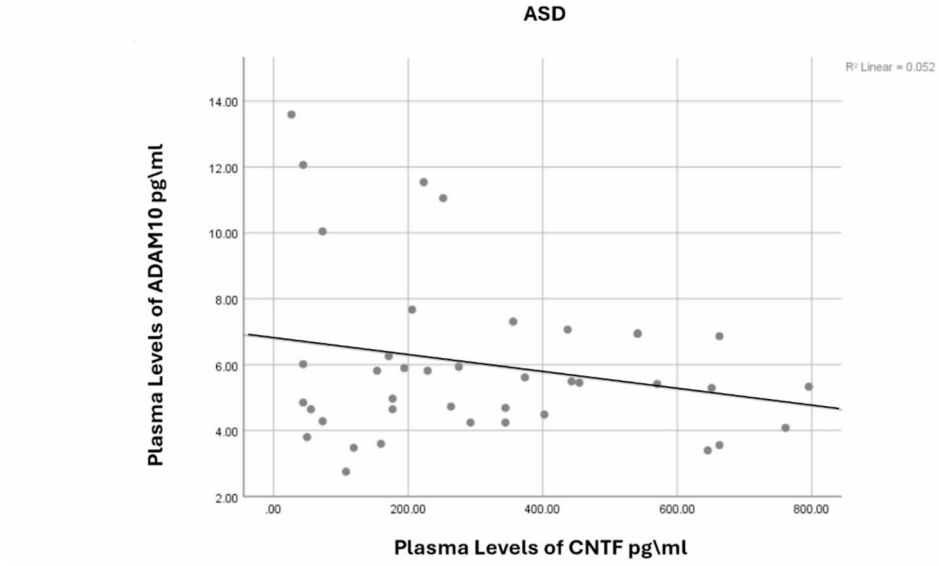


Fig. 4. (**A**) Regression analysis showed a positive correlation between cognitive function biomarker (ADAM10) and retina function biomarker (CNTF) in neurotypical children. (**B**) regression analysis showed a negative correlation between cognitive function biomarker (ADAM10) and retina function biomarker (CNTF) in ASD children.

Data availability

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

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Author contributions
S.M wrote the main manuscript, Conceptualization, Validation, methodologyL.A did the Investigation, Supervision, Funding acquisitionN.E wrote a manuscript draft A.A and T.H did Data Curation and Methodology A.M. did the Formal analysis and InvestigationA.H did the statistical analysis.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
Institutional Review Board and Guidelines of Health Sciences Colleges Research on Human Subjects, King Saud University, College of Medicine approved this study in accordance with the Declaration of Helsinki (Ref. No. 22/0122/IRB) in accordance with relevant guidelines. Informed consent was obtained from all participants' parents or legal guardians before they participated in approving the processing and publishing of data.

Additional information
Correspondence and requests for materials should be addressed to S.A.-M.