

Abnormal Brain Perfusion in Autism Spectrum Disorder: Evidence from Radionuclide SPECT Imaging

¹Sheikh Mohammad Adnan, ²Nasreen Sultana, ³Mohammed Badrul Alam, ⁴Shamsun Nahar Bailey, ⁵Khansa Tabassum Bushra, ⁶Md. Saiful Islam

¹Major, Combined Military Hospital, Dhaka, ²CMO, National Institute of Nuclear Medicine & Allied Sciences (NINMAS), BAEC.

³Assistant Professor, Department of Anesthesia, Analgesia and intensive care unit, BMU, ⁴SMO, NINMAS, BAEC.

⁵Assistant Professor, Biochemistry Department, Dhaka Medical College. Dhaka. ⁶Senior technologist, NINMAS

Correspondence Address: Major Dr. Sheikh Mohammad Adnan, Radiology imaging and Nuclear Medicine Department, Combined Military Hospital Dhaka. Email: sheikhmdadnan8@gmail.com, Cell: +8801717028745

ABSTRACT

Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition with increasing prevalence worldwide. Identifying cerebral perfusion abnormalities may provide objective biomarkers for diagnosis and therapeutic monitoring.

Objective: To evaluate regional cerebral blood flow (rCBF) abnormalities in children with ASD using Tc-99m ECD Brain SPECT and assess their correlation with clinical severity.

Methods: A cross-sectional study was conducted at the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Dhaka. A total of 34 children (3–12 years) with clinically confirmed ASD were included. Participants underwent ^{99m}Tc- ECD Brain SPECT, and perfusion abnormalities were analyzed using Z-scores. Severity was classified according to Autism Diagnostic Checklist (ADCL) scores. Statistical analysis was performed using SPSS v26, with $p \leq 0.05$ considered significant.

Results: Hypoperfusion was observed across multiple cortical regions. In mild ASD, hypoperfusion occurred in the frontal (100%), temporal (80%), and parietal (70%) cortices. Low-moderate ASD demonstrated widespread perfusion deficits, particularly in frontal (100%) and temporal (90%) regions. High-moderate ASD cases exhibited marked hypoperfusion in parietal (100%) and frontal (85%) regions. Symptom analysis revealed strong associations: speech delay (93%) correlated with frontal (98%) and temporal (88%) hypoperfusion; hyperactivity (68%) with frontal (100%) and temporal (85%) hypoperfusion; and cognitive dysfunction with frontal and parietal hypoperfusion. ADCL scores positively correlated with Z-scores ($\rho = 0.609$, $p = 0.002$). High-moderate ASD cases showed significantly elevated Z-scores compared to mild and low-moderate groups ($p < 0.05$).

Conclusion: Abnormal cerebral perfusion, particularly hypoperfusion in the frontal, temporal, and parietal cortices, is strongly associated with ASD severity and core clinical symptoms. Tc-99m ECD Brain SPECT may serve as a valuable adjunctive tool for early diagnosis, severity stratification, and therapeutic monitoring in ASD.

Keywords: Autism Spectrum Disorder, Brain SPECT, Cerebral Perfusion, Tc-99m ECD, Hypoperfusion.

Bangladesh J. Nucl. Med. Vol. 28 No. 2 July 2025

DOI: <https://doi.org/10.3329/bjnm.v28i2.89150>

INTRODUCTION

Autism Spectrum Disorder (ASD) is a multifaceted neurodevelopmental condition characterized by

persistent deficits in social communication and interaction, accompanied by restricted, repetitive patterns of behavior, interests, or activities. The global prevalence of ASD has been steadily increasing over the past two decades, with the World Health Organization estimating a frequency of approximately 1 in 150 children worldwide (1). South Asian epidemiological studies suggest regional variability, and Bangladeshi surveys have reported prevalence rates ranging from 0.15% to 0.8% (2,3). Despite this growing public health concern, diagnosis in most clinical settings continues to rely heavily on behavioral observation, caregiver interviews, and standardized screening tools based on the DSM-5 criteria. While these instruments are indispensable, they lack objective biological markers, resulting in diagnostic challenges, particularly in younger children and in resource-limited settings where expertise in behavioral assessment is scarce. This underscores the need for complementary approaches that can elucidate the underlying neurobiology of ASD and potentially serve as adjunctive diagnostic tools.

In recent years, neuroimaging has emerged as a promising avenue for understanding ASD pathophysiology. Structural imaging modalities such as magnetic resonance imaging (MRI) have provided insights into volumetric changes in cortical and subcortical regions, but findings remain inconsistent across studies. Functional techniques, in contrast, offer dynamic information about cerebral physiology. Among these, perfusion imaging has attracted particular interest, as regional cerebral blood flow (rCBF) is tightly coupled to neuronal activity and synaptic function. Measurement of rCBF therefore provides an indirect but robust marker

of functional brain integrity. Nuclear medicine techniques such as single-photon emission computed tomography (SPECT) using technetium-99m ethyl cysteinate dimer (Tc-99m ECD) are especially well suited for this purpose because of their ability to capture perfusion patterns under near-resting conditions with high sensitivity.

A substantial body of international research has demonstrated consistent patterns of cerebral perfusion abnormalities in children with ASD. The most frequently reported finding is hypoperfusion in the frontal, temporal, and parietal cortices (4–6). These regions are known to subserve higher-order cognitive and social processes—frontal lobes contribute to executive functions such as planning and impulse control, temporal regions are critical for language and social cognition, while the parietal cortex integrates sensory information and supports visuospatial awareness. Deficits in these domains align closely with the core clinical features of ASD, strengthening the biological plausibility of these imaging findings. Some studies have further suggested correlations between the degree of hypoperfusion and symptom severity, implying that perfusion imaging might not only assist in diagnosis but also provide prognostic information and help monitor therapeutic interventions (4–7).

Despite these promising observations, evidence from South Asia remains scarce. Cultural differences, genetic diversity, and variations in environmental exposures highlight the importance of conducting region-specific studies, as findings from Western populations may not be directly generalizable. Bangladesh, with its significant burden of ASD, represents an important setting for such investigations. Yet, systematic research exploring functional neuroimaging correlates in Bangladeshi children with ASD has been limited. Moreover, the availability of nuclear medicine facilities capable of performing SPECT imaging provides a unique opportunity to bridge this gap.

The present study was therefore designed to evaluate regional cerebral blood flow abnormalities in Bangladeshi children diagnosed with ASD using Tc-99m ECD brain SPECT imaging. In addition to describing perfusion patterns, the study aims to examine correlations between rCBF abnormalities and the severity of clinical symp-

toms, thereby contributing to the understanding of ASD pathophysiology in the local population. Establishing such correlations may support the use of perfusion imaging as a complementary diagnostic and research tool, potentially guiding earlier interventions and more individualized therapeutic approaches in resource-constrained environments.

PATIENTS AND METHODS

Study Design and Setting

This cross-sectional observational study was conducted at the National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Dhaka, a tertiary-level facility with advanced nuclear medicine imaging capabilities. The primary objective was to evaluate regional cerebral blood flow (rCBF) abnormalities in children with autism spectrum disorder (ASD) using Tc-99m ECD brain SPECT and to explore correlations with symptom severity.

Participants

A total of thirty-four children were enrolled through purposive sampling between 2022 and 2024. The study population consisted of 25 males and 7 females, with an age range of 3–12 years (mean age 7 years). All participants had a clinically confirmed diagnosis of ASD based on the DSM-IV or DSM-5 criteria, following comprehensive clinical evaluation and neurodevelopmental assessment.

Inclusion criteria comprised confirmed ASD diagnosis, while exclusion criteria included:

- Abnormal findings on computed tomography (CT) or magnetic resonance imaging (MRI),
- History of recurrent or persistent seizures,
- Known metabolic, chromosomal, or infectious neurological disorders.

These criteria were applied to ensure that perfusion abnormalities were attributable to ASD rather than coexisting neurological conditions.

Ethical Considerations

Ethical approval was obtained from the NINMAS Ethics Committee

(Ref: 39.01.2675.252.099.26.2013#55). Written informed

consent was secured from parents or legal guardians prior to participation. The study followed the ethical principles of the Declaration of Helsinki and institutional guidelines for research involving children.

Imaging Protocol

All participants underwent brain perfusion SPECT using technetium-99m ethyl cysteinate dimer (Tc-99m ECD) as the radiotracer. Each child received an intravenous injection of 2–3 millicuries (mCi) Tc-99m ECD. For patients unable to remain still, low-dose sedation was administered under close monitoring. Oxygen saturation (SpO₂) and heart rate (HR) were continuously monitored throughout the procedure to ensure patient safety.

Image acquisition began approximately 10 minutes after tracer injection to allow optimal distribution and uptake. Scans were obtained using a dual-head gamma camera system, ensuring high-resolution image quality (Figure 1).



Figure 1: Dual-head gamma camera system along performing brain SPECT study in a child with autism spectrum disorder at NINMAS, Dhaka

Image Processing and Quantitative Analysis

The acquired data were reconstructed and analyzed using eZIS (easy Z-score Imaging System) software, which provides voxel-based quantitative comparison of patient data against a normative age-matched database. Results were expressed as Z-scores, with negative deviations indicating regional hypoperfusion. This method enabled objective quantification of cerebral perfusion abnormalities in different cortical regions.

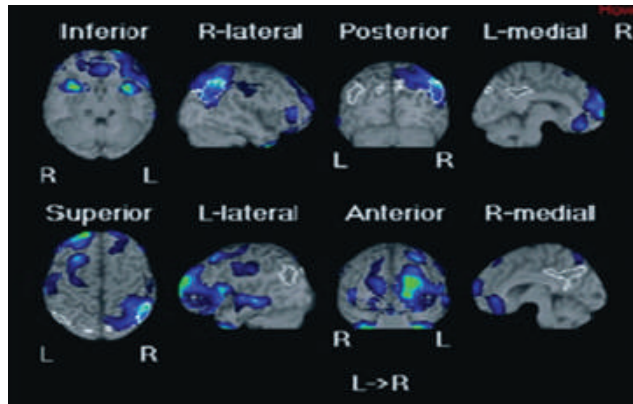


Figure 2: Multiple areas of hypoperfusion in cerebral cortex after eZIS software application

Clinical Assessment

Clinical severity of ASD was graded using the Autism Diagnostic Checklist (ADCL), a structured tool assessing social, communication, and behavioral domains. The checklist allowed classification of patients into varying severity categories, which were subsequently compared with imaging findings.

Statistical Analysis

All statistical analyses were performed using standard software. The Kruskal–Wallis test was applied to compare perfusion abnormalities across groups with different severity levels of ASD. Spearman’s rank correlation coefficient was used to examine associations between perfusion abnormalities (Z-scores) and clinical severity scores. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Clinical Profile

A total of 34 children with autism spectrum disorder (ASD) were included in this study, comprising 25 male and 9 female, yielding a male-to-female ratio of 3:1. This gender distribution is consistent with the well-documented male predominance in ASD. The clinical symptom profile revealed that the most frequent presenting complaint was speech delay, observed in (n= 31), 93% of cases. This was followed by hyperactivity (n= 23), 68%, poor eye contact (n= 14), 40% and cognitive dysfunction (n=15), 45%. Many children exhibited overlapping symptoms, with speech delay and hyperactivity being the most common coexisting features.

Perfusion Abnormalities by Severity

Perfusion abnormalities on Tc-99m ECD brain SPECT were stratified according to the severity of ASD, as determined by ADCL grading.

- **Mild ASD (n = 15):** Patients with mild severity consistently demonstrated frontal hypoperfusion (100%), indicating early involvement of regions responsible for executive functioning and social interaction (Figure 2). Additional perfusion deficits were seen in the temporal lobes (80%) and parietal lobes (70%), though these were less uniform (Figure 3).
- **Low-Moderate ASD (n= 12):** In this subgroup, perfusion abnormalities were more widespread. All cases showed frontal (100%) and temporal (90%) hypoperfusion, while parietal deficits were present in 88% of patients. These findings suggest progressive involvement of cortical networks with increasing symptom burden.
- **High-Moderate ASD (n =07):** Children in this category exhibited the most pronounced abnormalities, with severe parietal hypoperfusion (100%) and extensive frontal deficits (84%). The extent and severity of perfusion deficits were markedly greater than those observed in the mild and low-moderate subgroups, reflecting a strong association between perfusion abnormalities and clinical severity.

The bar diagram shows regional hypoperfusion percentages in mild, low-moderate, and high-moderate ASD. Frontal and temporal hypoperfusion were consistently observed across all groups, while parietal involvement increased with severity and became universal in high-moderate cases. Precuneus and cingulate gyri abnormalities appeared predominantly in more severe ASD, indicating progressive cortical involvement.

Symptom-Perfusion Correlation

A detailed analysis of symptom-specific correlations further supported the central role of cortical hypoperfusion in ASD manifestations:

- **Speech delay** was strongly associated with perfusion deficits in the frontal cortex (98%) and temporal cortex (88%), reflecting the involvement of brain regions crucial for speech generation, language comprehension, and communication.
- **Hyperactivity** showed a uniform correlation with frontal lobe hypoperfusion (100%), along with notable involvement of the temporal lobes (85%). These findings align with the known role of the prefrontal and temporal circuits in attention and behavioral regulation.
- **Cognitive** dysfunction correlated strongly with deficits in the frontal cortex (100%) and parietal cortex (90%), indicating that higher-order executive and visuospatial domains are disproportionately impacted in ASD children with intellectual impairments.

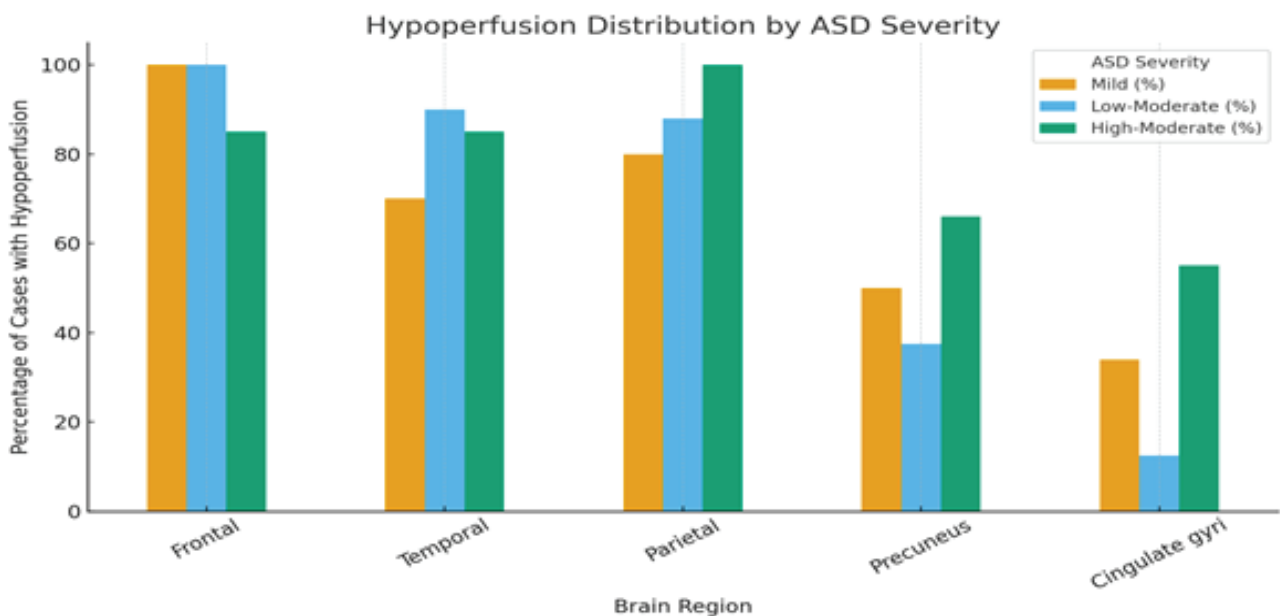


Figure 3. Hypoperfusion distribution across brain regions by ASD severity

- Poor eye contact**, a hallmark social deficit in ASD, was associated with hypoperfusion in both the frontal cortex (90%) and the parietal cortex (78%), regions implicated in social cognition, visual attention, and face-processing networks. (Figure 4).

The bar diagram shows the percentage of cases with regional hypoperfusion associated with speech delay, hyperactivity, cognitive dysfunction, and poor eye contact. Frontal and temporal cortices were most consistently affected across all symptom domains, while parietal hypoperfusion was strongly linked to cognitive dysfunction. Precuneus involvement was less frequent but present across all symptoms.

These correlations underscore that specific clinical manifestations are linked to distinct cortical perfusion deficits, strengthening the biological plausibility of the imaging findings.

The Kruskal–Wallis test was performed to compare Z-scores across severity groups (Mild, Low moderate, High moderate) (Figure 5). There was a statistically significant difference ($H = 8.90, df = 2, p = 0.012$). Post-hoc Bonferroni analysis revealed that the High moderate group had significantly higher Z-scores than both the Mild ($p = 0.004$) and Low moderate groups ($p = 0.009$). No significant difference was found between Mild and Low moderate groups ($p = 1.000$).

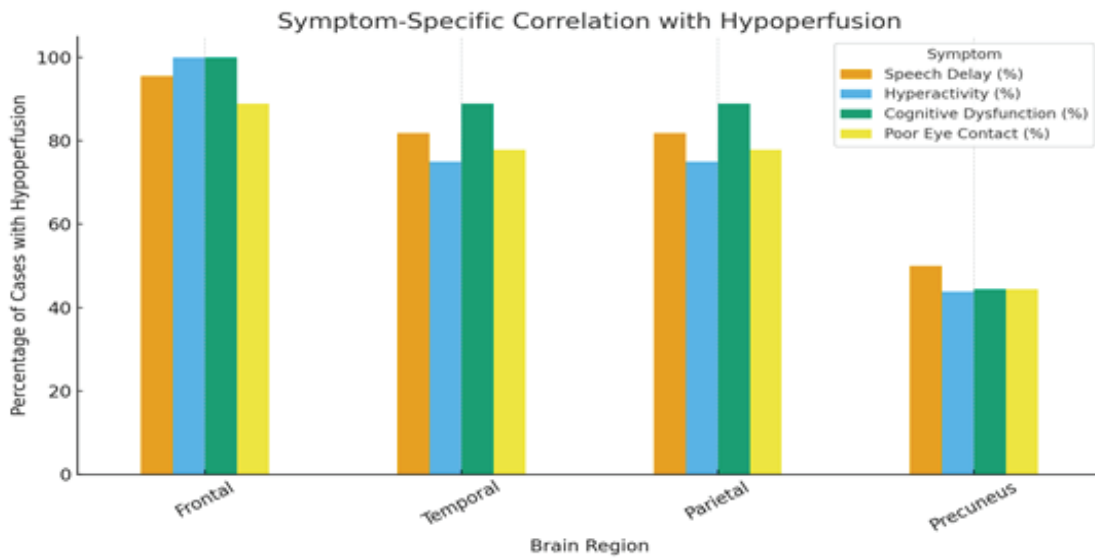


Figure 4. Symptom-specific correlation of hypoperfusion with core ASD symptoms

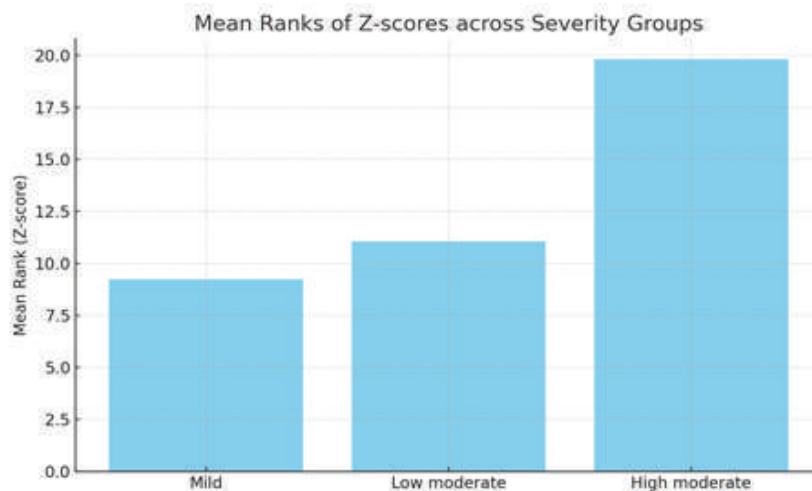


Figure 5. Mean ranks of Z-scores across severity groups

Spearman's correlation Quantitative analysis revealed a significant positive correlation between ADCL severity scores and perfusion abnormalities as measured by Z-scores ($\rho = 0.609$, $p = 0.002$). This indicates that children with more severe ASD symptoms exhibited more profound cerebral hypoperfusion.

When comparing perfusion deficits across severity groups, children with high-moderate ASD had significantly greater perfusion abnormalities compared to both mild and low-moderate groups ($p < 0.05$). These findings confirm that the severity of cortical perfusion deficits parallels the clinical severity of ASD.

Taken together, these results demonstrate that the frontal cortex is the most consistently and severely affected region across all severity levels of ASD, while the temporal and parietal lobes show progressive involvement with increasing severity. Symptom-specific correlations further highlight the neurobiological underpinnings of clinical features such as speech delay, hyperactivity, poor eye contact, and cognitive dysfunction. Moreover, the statistically significant association between ADCL scores and perfusion abnormalities underscores the clinical relevance of brain perfusion SPECT as a valuable complementary tool in the comprehensive assessment of ASD.

DISCUSSION

This study demonstrated reproducible, severity-dependent patterns of cerebral hypoperfusion in children with ASD. The most frequently affected regions were the frontal, temporal, and parietal cortices, which correspond closely to the domains of executive functioning, language, social cognition, and visuospatial processing—core areas of impairment in ASD. Importantly, the degree of hypoperfusion increased with symptom severity, supporting the concept that regional cerebral blood flow abnormalities reflect not only the presence but also the progression of clinical deficits in ASD.

Our findings are consistent with prior international studies, reinforcing the universality of perfusion abnormalities in ASD pathophysiology. Studies reported prefrontal and temporal cortical hypoperfusion in children with ASD, findings replicated across multiple independent cohorts (8, 9). Similar reports were also

demonstrated, where abnormal hemispheric asymmetry and reduced rCBF in temporal regions using SPECT, linked those abnormalities to impaired social communication, a finding corroborated by various independent cohorts (10, 11). Few authors highlighted frontal lobe dysfunction as a hallmark of ASD, describing it as a “frontal disconnection syndrome” affecting higher-order integrative functions (7).

South Asian researchers reported widespread perfusion abnormalities in Indian children with ASD, including both cortical and subcortical regions, with severity-dependent changes resembling those observed in our cohort (6). The convergence of findings across diverse populations suggests that cerebral hypoperfusion is not an isolated regional phenomenon but a robust marker of ASD-related neurobiological dysfunction.

The symptom-perfusion correlations observed in this study provide compelling evidence for the neurobiological underpinnings of clinical manifestations. Speech delay, the most frequent presenting symptom, was strongly associated with frontal and temporal hypoperfusion, implicating networks involved in expressive language, semantic processing, and working memory. These results align with Ohnishi et al. (5) and Ratnam BV et al. (12) who demonstrated reduced activation in Broca's and Wernicke's homologous regions in children with ASD.

Hyperactivity was universally correlated with frontal lobe deficits, consistent with the role of the prefrontal cortex in inhibitory control, attention, and impulse regulation. This was previously demonstrated as delayed frontal maturation in ASD, potentially contributing to attentional dysregulation (4).

Cognitive dysfunction was most strongly associated with combined frontal and parietal hypoperfusion, reflecting disruption of fronto-parietal networks critical for executive function and working memory. Finally, poor eye contact, a defining social deficit, was associated with hypoperfusion in both frontal and parietal cortices, regions implicated in gaze processing and visuospatial attention, supporting functional MRI studies showing reduced activation in the “social brain” network during eye-contact tasks (13-17).

The diagnosis of ASD remains behaviorally driven, reliant on DSM-5 criteria and structured interviews. Although these methods are well-established, they lack objective biomarkers and are susceptible to variability based on cultural context, caregiver reporting, and examiner expertise. The results of this study suggest that brain perfusion SPECT could serve as a valuable complementary tool, particularly in resource-limited settings such as Bangladesh, where advanced neuroimaging modalities like fMRI or PET are less accessible.

Beyond diagnosis, perfusion imaging may have significant value in monitoring therapeutic interventions. Several studies have demonstrated normalization of rCBF following behavioral therapy or pharmacological treatment, correlating with clinical improvement (18-22). Thus, SPECT has potential utility in both tracking treatment response and providing prognostic insights.

CONCLUSION

This study demonstrates that ^{99m}Tc- ECD brain SPECT reliably identifies severity-dependent patterns of regional cerebral hypoperfusion in children with ASD in Bangladesh. The most consistently affected regions were the frontal, temporal, and parietal cortices, which correspond to the domains of executive functioning, language, and social cognition. The observed perfusion deficits showed a significant correlation with clinical severity and specific symptomatology, highlighting the neurobiological basis of behavioral manifestations in ASD. These findings support the utility of brain perfusion SPECT as a potential functional biomarker for the diagnosis, severity stratification, and longitudinal monitoring of ASD, particularly in resource-limited settings where advanced functional imaging modalities may not be widely accessible.

LIMITATION

The study acknowledges several limitations including a small sample size from a single center, potentially affecting the generalizability of results. The possibility of residual confounding remains despite efforts to exclude patients with brain abnormalities and comorbid disorders. A cross-sectional design limits the ability to infer causal relationships regarding perfusion abnormalities.

Furthermore, while SPECT imaging is valuable, its spatial resolution is inferior to PET or fMRI. Future research should focus on larger, multicenter studies with longitudinal designs to assess cerebral perfusion changes. Integrating SPECT with other imaging modalities and biological markers may enhance understanding of ASD neurobiology, with studies needed to explore the effects of treatments on perfusion patterns for better diagnostic and prognostic capabilities.

Competing Interests

The authors declare no conflicts of interest.

ACKNOWLEDGEMENT

IPNA and Department of Anesthesia, Analgesia and intensive care unit, BMU.

FINANCIAL DISCLOSURE

This study was partially funded by a grant from R&D, The Ministry of Science and Technology, Bangladesh

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