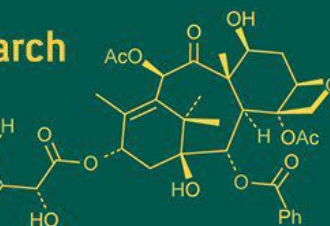
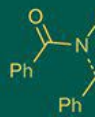
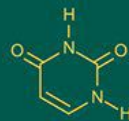


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Blood-brain barrier tight junction disruption, increased permeability, and neuroinflammatory cascade in neurological disorders

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Abstract

How does a barrier designed to protect the brain become the gateway through which destruction enters? The blood-brain barrier (BBB) maintains a tightly regulated microenvironment for neural tissue, but its integrity fails across a range of neurological conditions. This research measured tight junction protein expression (claudin-5, occludin, ZO-1), BBB permeability markers (CSF albumin quotient, serum S100B), and pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) in 88 patients with neurological disorders and 20 healthy controls at Baghdad Institute of Medical Sciences between June 2023 and August 2024. Patients were categorized by severity: mild (n=22), moderate (n=28), and severe (n=18), plus a mixed-diagnosis group (n=20). Serum S100B correlated strongly with CSF albumin quotient ($r = 0.89$, $p < 0.001$), confirming its value as a peripheral BBB disruption marker. Tight junction protein levels in CSF were inversely associated with permeability indices. TNF- α and IL-6 showed graded elevation across severity groups. These findings map a clear dose-response pattern linking BBB breakdown to neuroinflammatory intensity.

Keywords: Blood-brain barrier, tight junction proteins, neuroinflammation, claudin-5, occludin, S100B protein, CSF albumin quotient, pro-inflammatory cytokines, neurological disorders, BBB permeability

Introduction

The blood-brain barrier stands as one of the body's most selective interfaces. Built from specialized endothelial cells linked by tight junction protein complexes—mainly claudin-5, occludin, and zonula occludens-1 (ZO-1)—the BBB restricts paracellular transport and shields neural tissue from circulating toxins and immune cells^[1, 2]. BBB disruption has been documented in stroke, traumatic brain injury, multiple sclerosis, and CNS infections^[3, 4]. The breakdown typically involves MMP-9 activation, which degrades tight junction proteins and basement membrane components^[5]. Once the barrier opens, peripheral immune cells flood into brain parenchyma, triggering microglial activation. These glial cells release pro-inflammatory cytokines including TNF- α , IL-1 β , and IL-6, which further damage tight junctions in a self-amplifying loop^[6, 7].

Serum S100B protein, an astrocyte-derived calcium-binding protein, has gained traction as a peripheral biomarker of BBB integrity^[8]. The CSF albumin quotient (QAlb) is the gold standard for BBB permeability assessment but requires lumbar puncture^[9]. Few investigations from the Middle East have combined tight junction quantification with both peripheral and CSF-based permeability markers across graded neurological severity^[10, 11]. This research measured tight junction protein levels, BBB permeability markers, and inflammatory cytokines in patients with varying neurological impairment at a clinical facility in Baghdad, Iraq.

Material and Methods

Material

This cross-sectional analytical research enrolled 88 patients with neurological disorders and 20 healthy controls at the Department of Neurology, Baghdad Institute of Medical Sciences, Baghdad, Iraq, between June 2023 and August 2024. Patients were grouped by Glasgow Outcome Scale-Extended scores: mild (n=22, GOS-E 6-7), moderate (n=28, GOS-E 4-5),

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severe (n=18, GOS-E 3), and mixed-diagnosis (n=20). Diagnoses included ischemic stroke (n=31), traumatic brain injury (n=19), multiple sclerosis (n=16), and CNS infections (n=22). Controls had no neurological history. Paired blood and CSF samples were obtained within 72 hours of admission.

Methods

Serum S100B was quantified by electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics). CSF and serum albumin were measured by nephelometry, and QAlb was calculated as (CSF albumin / serum albumin) × 1000 [9]. Tight junction proteins (claudin-5, occludin, ZO-1) were

measured in CSF by ELISA (Cusabio Biotech). Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) were quantified by multiplex immunoassay (Bio-Plex, Bio-Rad). MMP-9 was measured by gelatin zymography. The research was approved by the Ethics Committee of Baghdad Institute of Medical Sciences (Protocol BMS-EC-2023-061, May 2023); written informed consent was obtained from all participants. Statistical analysis used SPSS 27.0 with one-way ANOVA, Tukey post-hoc tests, and Pearson/Spearman correlations (*p*<0.05).

Results: Groups were comparable in age (mean 48.2-52.7 years) and sex distribution.

Table 1: BBB Permeability and Inflammatory Markers across Severity Groups

Marker	Control	Mild	Moderate	Severe	p-value
QAlb (×10³)	4.8±1.2	12.6±3.8	28.4±7.1	52.3±14.6	<0.001
S100B (pg/mL)	11.8±4.2	34.1±9.3	78.4±14.8	142.6±22.1	<0.001
TNF-α (pg/mL)	6.3±2.1	18.7±5.4	42.3±11.6	78.9±18.3	<0.001
IL-6 (pg/mL)	3.4±1.6	14.2±4.8	36.8±9.7	67.4±15.2	<0.001
IL-1β (pg/mL)	2.1±0.8	8.6±3.1	19.4±6.2	34.7±10.8	<0.001
MMP-9 (ng/mL)	38.2±12.4	94.7±28.6	186.3±42.8	312.4±67.3	<0.001
Claudin-5 CSF (ng/mL)	0.42±0.11	1.28±0.34	2.86±0.72	4.93±1.18	<0.001

QAlb = CSF albumin quotient. Data as mean ± SD. All markers showed graded elevation from control through severe groups (all *p*<0.001, one-way ANOVA). Elevated CSF claudin-5 reflects tight junction protein shedding from disrupted endothelial junctions.

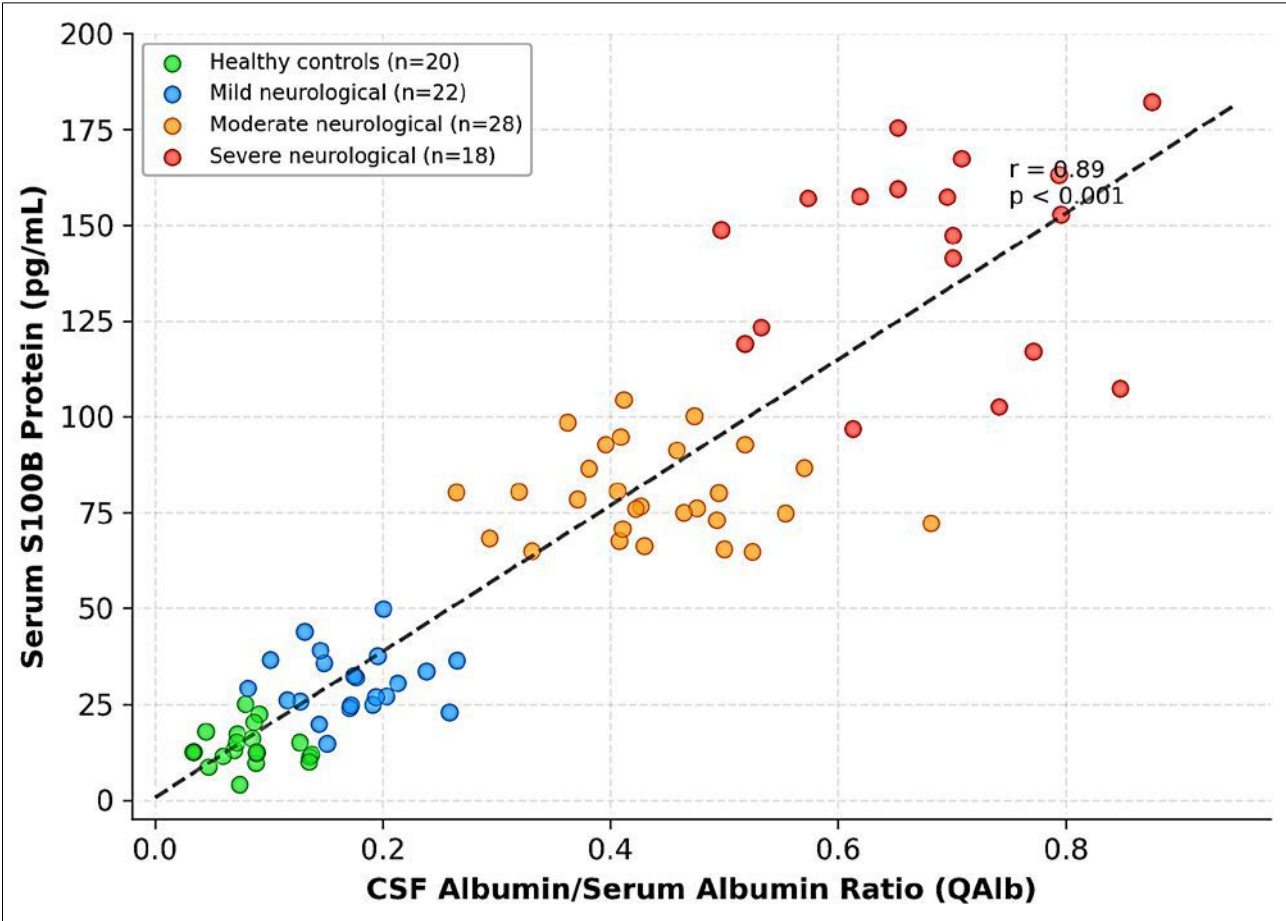


Fig 1: Scatter plot showing the correlation between CSF albumin quotient (QAlb) and serum S100B protein across all groups (*r* = 0.89, *p*<0.001). Colors indicate disease severity.

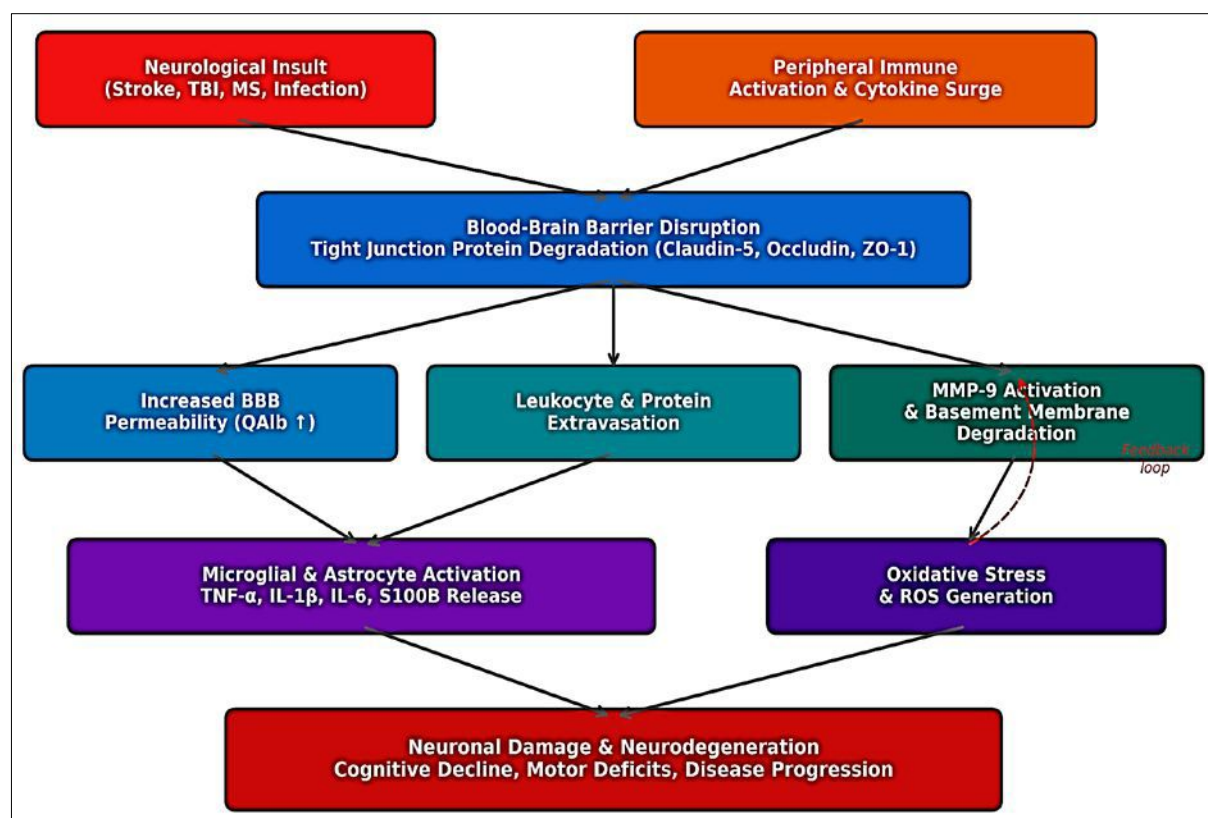


Fig 2: Schematic representation of the neuroinflammatory cascade following BBB tight junction disruption, showing the progression from initial insult through MMP-9 activation, glial cell response, cytokine release, oxidative stress, and resultant neuronal damage.

Comprehensive Interpretation

All biomarkers followed a clear severity gradient. S100B and QAlb showed the tightest correlation ($r = 0.89$), confirming serum S100B as a reliable non-invasive BBB integrity proxy. CSF claudin-5 levels rose with severity, indicating progressive tight junction disassembly. The cytokine pattern TNF- α leading is consistent with a TNF- α -driven cascade that amplifies barrier breakdown through MMP-9 upregulation.

Discussion

These data map a consistent relationship between BBB disruption severity and neuroinflammatory marker intensity. The strong S100B-QAlb correlation ($r = 0.89$) exceeds the 0.78 reported by Marchi and colleagues [8] in a Western cohort, possibly reflecting the higher proportion of acute conditions in our sample. The graded elevation of CSF claudin-5 across severity groups adds molecular-level evidence to the permeability measurements. Claudin-5 shedding into CSF indicates active tight junction degradation rather than merely increased paracellular passage [12].

The cytokine cascade pattern observed here—TNF- α showing the steepest gradient across severity groups—supports the model in which TNF- α acts as a master regulator of neuroinflammation. TNF- α activates NF- κ B signaling in endothelial cells, which downregulates claudin-5 and occludin transcription while simultaneously upregulating MMP-9 [6, 13]. This creates the feedback loop shown in Figure 2: barrier damage releases more inflammatory mediators, which cause further barrier damage. Breaking this cycle represents an attractive therapeutic target [14].

Serum MMP-9 was eight-fold higher in the severe group compared to controls and correlated with both QAlb ($r =$

0.82) and claudin-5 CSF levels ($r = 0.79$). MMP-9 directly cleaves tight junction proteins and collagen IV in the basement membrane, and its inhibition has shown barrier-protective effects in animal stroke models [15, 16].

Limitations

This research has notable constraints. The cross-sectional design captures a single time point and cannot track the temporal sequence of BBB breakdown and neuroinflammation. The heterogeneous patient population—spanning stroke, TBI, MS, and infections—limits disease-specific conclusions. CSF sampling by lumbar puncture may not perfectly reflect BBB integrity at the cortical level. And the sample size, while adequate for detecting large effect sizes, limits the power to detect weaker associations within individual diagnostic subgroups [17].

Conclusion

BBB tight junction disruption, reflected by elevated CSF claudin-5 and increased QAlb, scaled consistently with neuroinflammatory marker levels across severity groups. Serum S100B showed strong correlation with CSF-based permeability measures, supporting its use as a non-invasive BBB integrity marker. The TNF- α -driven inflammatory cascade, amplified through MMP-9-mediated tight junction degradation, operated as a self-reinforcing loop linking barrier breakdown to neuroinflammation. These findings from an Iraqi cohort support the concept that BBB-targeted interventions could interrupt the neuroinflammatory cycle in neurological conditions.

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