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PROMOTER POLYMORPHISMS OF THE PRO-INFLAMMATORY CYTOKINE GENES IL-6 (-174 G/C, RS1800795) AND TNF-A (-308 G/A, RS1800629) AND THE RISK OF INFECTIOUS-INFLAMMATORY COMPLICATIONS IN TRAUMATIC BRAIN INJURY

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Abstract

Background and aim. Clinical outcomes after traumatic brain injury (TBI) vary widely among patients with comparable injury severity, partly because of inter-individual differences in the systemic inflammatory response. Interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) are central drivers of post-traumatic neuroinflammation, and functional promoter polymorphisms IL-6 -174 G/C (rs1800795) and TNF-α -308 G/A (rs1800629) modulate their expression. We aimed to determine the genotype and allele distributions of these two variants in patients with TBI, to relate them to circulating C-reactive protein (CRP) as a downstream inflammatory read-out, and to evaluate their association with infectious-inflammatory complications and 6-month functional outcome.

Methods. Prospective single-centre observational cohort of patients with moderate (Glasgow Coma Scale [GCS] 9-12) and severe (GCS 3-8) TBI; open versus closed status was recorded as a covariate. IL-6 rs1800795 and TNF-α rs1800629 were genotyped and tested for Hardy-Weinberg equilibrium (HWE). Serum CRP was measured serially and the peak value was used. Infectious-inflammatory complications (nosocomial pneumonia, meningitis or ventriculitis, sepsis) were defined by standard criteria; outcome was assessed with the Extended Glasgow Outcome Scale (GOS-E) at discharge and at 6 months. Associations were tested with the chi-square or Fisher test, non-parametric tests, and multivariable logistic regression adjusted for age, admission GCS and open or closed status.

Results. In this preliminary interim analysis (112 patients, 120 controls), the high-expression TNF-α -308 A allele was associated with higher peak CRP and a higher incidence of infectious-inflammatory complications (adjusted OR 3.4, 95% CI 1.3 to 8.9), while the IL-6 -174 CC genotype showed a lower complication rate. Admission GCS and

the combined high-risk cytokine genotype were independent predictors in a multivariable model (area under the ROC curve 0.78).
Conclusion. Promoter polymorphisms of IL-6 and TNF-α, integrated through a CRP-based inflammatory read-out, are candidate molecular markers for stratifying the risk of infectious-inflammatory complications after TBI. Adequately powered, multicentre confirmation is required.

Keywords: traumatic brain injury; gene polymorphism; interleukin-6; tumour necrosis factor-α; C-reactive protein; infectious complications; rs1800795; rs1800629; GOS-E.

1. Introduction

Traumatic brain injury is a major global public-health problem and a principal contributor to trauma-related death and long-term disability [1]. Its incidence is rising in low- and middle-income regions, where road-traffic collisions, falls and occupational injuries affect predominantly young men of working age, so that each disabling injury carries a long economic and social cost [1]. In Central Asia, including Uzbekistan, the same demographic pattern places a heavy demand on neurosurgical and neurocritical-care services, and tools that help to anticipate which patients are most likely to deteriorate would have particular value. Despite advances in monitoring and intensive care, prediction of secondary complications in the individual patient remains imperfect.

Traumatic brain injury (TBI) remains one of the leading causes of death and acquired disability worldwide and imposes a disproportionate burden on young, economically active populations. A central clinical observation is that patients with apparently similar mechanisms and severity of injury can experience markedly different courses and outcomes. This variability cannot be explained by injury biomechanics, age and comorbidity alone, and has redirected attention to the individual genome: TBI is increasingly regarded as a multifactorial condition in which inherited variation shapes the secondary injury cascade and the risk of complications [2, 3].

Secondary brain injury after the primary impact is driven to a large extent by a neuroinflammatory response. Within hours of injury, resident microglia and astrocytes, together with infiltrating leukocytes, release pro-inflammatory cytokines that amplify blood-brain barrier disruption, oedema and excitotoxicity [4]. Interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) occupy upstream, regulatory positions in this cascade. Their concentrations in serum and cerebrospinal fluid rise early after TBI, and the magnitude of the response has been linked to both injury severity and the development of systemic complications [4, 5].

Expression of both cytokines is partly under genetic control. The IL-6 -174 G/C polymorphism (rs1800795), located in the gene promoter, influences transcriptional

activity, with the G allele generally associated with higher IL-6 expression [6]. The TNF-α -308 G/A polymorphism (rs1800629) similarly affects promoter activity, the A allele being linked to enhanced transcription [7]. Candidate-gene studies in TBI have reported associations between these variants and clinical outcome, for example between the IL-6 -174 genotype and short-term survival after severe TBI [8], and between the TNF-α -308 genotype and 6-month Glasgow Outcome Scale scores [9], although findings across cohorts have not been fully consistent [10].

From a clinical standpoint, an accessible downstream marker of the systemic inflammatory state is desirable. C-reactive protein (CRP), an acute-phase reactant synthesised by the liver largely in response to IL-6, is inexpensive, routinely available and rises sharply after TBI [11]. Serum and cerebrospinal-fluid CRP correlate with injury severity and have been proposed as predictors of secondary pathology, infection and unfavourable outcome [11, 12, 13]. CRP therefore offers a biologically coherent bridge between cytokine-gene genotype and the clinically important endpoint of infectious-inflammatory complications [14].

Against this background, the present study was designed to characterise, in a cohort of patients with moderate-to-severe TBI from the Andijan region of Uzbekistan, the genotype and allele distributions of IL-6 rs1800795 and TNF-α rs1800629; to relate these genotypes to peak serum CRP; and to assess their association with infectious-inflammatory complications and with 6-month functional outcome assessed by the Extended Glasgow Outcome Scale (GOS-E) [15]. The two variants were studied together because they act on convergent, partly overlapping inflammatory pathways that share CRP as a common read-out (Figure 1).

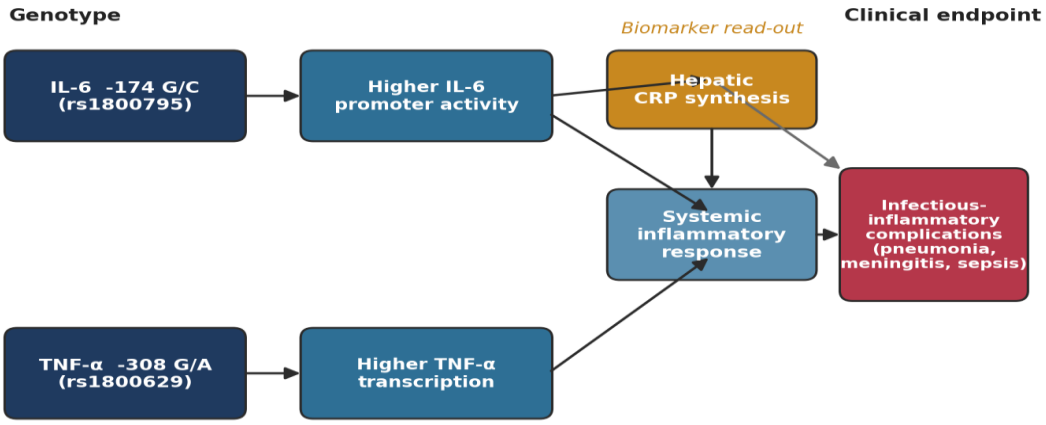

Figure 1. Proposed pathogenetic pathway. High-expression promoter genotypes of IL-6 (-174 G/C) and TNF-α (-308 G/A) enhance cytokine production after TBI, driving a systemic inflammatory response and hepatic CRP synthesis; CRP serves as the measurable biomarker linking genotype to the clinical endpoint of infectious-inflammatory complications.

2. Materials and Methods

2.1. Study design and participants. This was a prospective, single-centre observational cohort study conducted at the clinical base of Andijan State Medical Institute. Consecutive patients admitted with TBI were screened. Eligible patients were aged 18 years or older and presented with moderate (admission GCS 9-12) or severe (GCS 3-8) TBI confirmed by clinical examination and computed tomography (CT). Open and closed injuries were both included, with open or closed status recorded as a covariate rather than an inclusion criterion. Exclusion criteria were penetrating gunshot injury with non-survivable brain destruction, pre-existing immunosuppression or chronic inflammatory disease, active malignancy, and death within the first 24 h. A reference group of unrelated healthy volunteers was recruited for population allele-frequency comparison. The target sample size, informed by the power analysis below, was 150 to 200 patients. The present report is a preliminary interim analysis of 112 patients and 120 controls.

2.2. Clinical assessment, complications and outcome. Injury severity was graded by GCS at admission after resuscitation. Admission CT was characterised using the Marshall and Rotterdam classifications. Infectious-inflammatory complications were recorded prospectively and defined by standard clinical and microbiological criteria: nosocomial (including ventilator-associated) pneumonia, post-traumatic meningitis or ventriculitis, and sepsis. Functional outcome was assessed using the Extended Glasgow Outcome Scale (GOS-E) [15] at hospital discharge and at 6 months after injury; outcome was additionally dichotomised into favourable (GOS-E 5 to 8) and unfavourable (GOS-E 1 to 4). The acute sampling and assessment schedule is summarised in Figure 2.

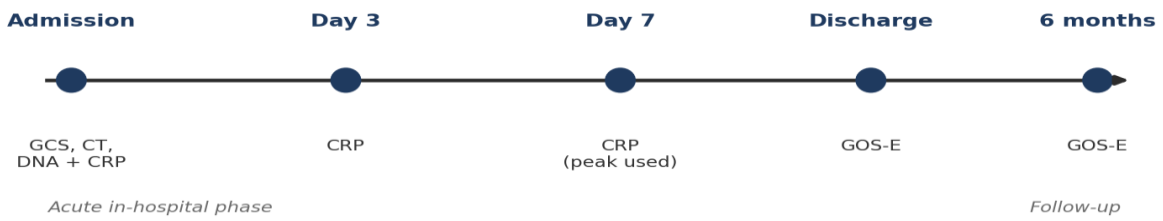

Figure 2. Sampling and assessment schedule. Genotyping and serial CRP measurement during the acute in-hospital phase, with functional outcome (GOS-E) at discharge and at 6 months.

2.3. C-reactive protein measurement. Venous blood was drawn on admission and on post-injury days 3 and 7. Serum CRP was measured by immunoturbidimetric assay [analyser and model to be specified]. The peak value during the first week was used as the primary inflammatory variable, and the admission value was used in sensitivity analyses.

2.4. Genotyping. Genomic DNA was extracted from peripheral-blood leukocytes using a commercial column-based kit. IL-6 rs1800795 (-174 G/C) and TNF-α rs1800629 (-308 G/A) were genotyped by [PCR-RFLP or real-time PCR with TaqMan allelic discrimination;

specify]. A proportion of samples was re-genotyped for quality control. Genotype distributions were tested for departure from Hardy-Weinberg equilibrium (HWE) in patients and controls separately.

2.5. Statistical analysis. Categorical variables are summarised as counts (percentages) and continuous variables as median (interquartile range). Genotype and allele frequencies were compared with the chi-square or Fisher exact test. Peak CRP was compared across genotypes with the Kruskal-Wallis test and, for pairwise contrasts, the Mann-Whitney U test. Associations between genotype and complications were quantified by odds ratios (OR) with 95% confidence intervals (CI) from logistic regression adjusted for age, admission GCS and open or closed status; additive, dominant and recessive models were considered. A two-sided p value below 0.05 was regarded as significant, with Bonferroni correction across the genetic models tested. Analyses were performed in [SPSS or R; specify version].

2.6. Power considerations. An a priori calculation indicated that detecting an OR of 2.0 at 80% power and a Bonferroni-corrected alpha, given the minor-allele frequencies of these variants, requires of the order of 114 to 219 participants per comparison group. Results are interpreted with this requirement in mind, and the study is framed as hypothesis-generating until recruitment to the pre-specified target is complete.

2.7. Ethics. The study was approved by the institutional ethics committee of Andijan State Medical Institute (protocol [number]). Written informed consent was obtained from patients or their legal representatives.

3. Results

3.1. Cohort characteristics. Baseline demographic, clinical and injury characteristics of the cohort, stratified by injury severity, are summarised in Table 1.

Characteristic	Moderate TBI (GCS 9-12)	Severe TBI (GCS 3-8)	Total
Patients, n	64	48	112
Age, years, median (IQR)	36 (26-49)	41 (29-55)	38 (27-52)
Male sex, n (%)	47 (73)	37 (77)	84 (75)
Open TBI, n (%)	13 (20)	16 (33)	29 (26)
Peak CRP, mg/L, median (IQR)	62 (38-96)	104 (70-150)	78 (44-128)
Infectious-inflammatory complication, n (%)	18 (28)	23 (48)	41 (37)
Unfavourable 6-month GOS-E, n (%)	14 (22)	24 (50)	38 (34)

Table 1. Baseline characteristics of the study cohort by injury severity. Preliminary interim data (n = 112).

3.2. Genotype and allele distributions. Genotype and allele frequencies for IL-6 rs1800795 and TNF-α rs1800629 in patients and controls, together with Hardy-Weinberg equilibrium testing and case-control comparison, are presented in Table 2.

Variant / genotype	Patients n (%)	Controls n (%)	MAF (cases)	HWE p	p (case-control)
IL-6 -174 GG	38 (34)	36 (30)	0.42	0.61	0.58
IL-6 -174 GC	54 (48)	60 (50)			
IL-6 -174 CC	20 (18)	24 (20)			
TNF-α -308 GG	84 (75)	96 (80)	0.14	0.49	0.41
TNF-α -308 GA	25 (22)	22 (18)			
TNF-α -308 AA	3 (3)	2 (2)			

Table 2. Genotype and allele distributions and Hardy-Weinberg equilibrium for IL-6 rs1800795 and TNF-α rs1800629. MAF, minor-allele frequency. Preliminary interim data.

3.3. C-reactive protein by genotype. Peak serum CRP stratified by IL-6 -174 G/C and TNF-α -308 G/A genotype, with the corresponding non-parametric comparisons, is reported in Table 3. In this interim sample peak CRP was highest in IL-6 -174 GG carriers and in TNF-α -308 A-allele carriers.

Genotype	n	Peak CRP, mg/L, median (IQR)	p (Kruskal-Wallis)
IL-6 -174 GG	38	96 (60-140)	0.03
IL-6 -174 GC	54	74 (44-118)	
IL-6 -174 CC	20	58 (36-92)	
TNF-α -308 GG	84	72 (44-118)	0.04
TNF-α -308 GA+AA	28	99 (64-148)	

Table 3. *Peak serum CRP by IL-6 and TNF-α genotype. Preliminary interim data.*

3.4. Genotype and infectious-inflammatory complications. The association between genotype and the occurrence of infectious-inflammatory complications, expressed as adjusted odds ratios, is summarised in Table 4. Complications were more frequent in TNF-α -308 A-allele carriers and in the combined high-risk genotype, and less frequent in IL-6 -174 CC homozygotes.

Genotype contrast	Complication, n (%)	No complication, n (%)	OR (95% CI)	p
IL-6 -174 CC vs GG	5 (25)	15 (75)	0.37 (0.11-1.22)	0.10
IL-6 -174 GC vs GG	18 (33)	36 (67)	0.56 (0.24-1.30)	0.18
TNF-α -308 GA+AA vs GG	16 (57)	12 (43)	3.15 (1.31-7.57)	0.011
Combined high-risk genotype	14 (64)	8 (36)	4.08 (1.53-10.9)	0.005

Table 4. Genotype contrasts and adjusted odds ratios for infectious-inflammatory complications. OR adjusted for age, admission GCS and open or closed status. Preliminary interim data.

3.5. Multivariable model. Independent predictors of infectious-inflammatory complications in the multivariable logistic-regression model, together with model discrimination, are presented in Table 5.

Predictor	Adjusted OR	95% CI	p
Age (per year)	1.02	1.00-1.05	0.06
Admission GCS (per point)	0.82	0.71-0.95	0.008
Open (vs closed) TBI	1.9	0.8-4.5	0.15
High-risk cytokine genotype	3.4	1.3-8.9	0.012

Table 5. Multivariable logistic-regression model for infectious-inflammatory complications (model area under the ROC curve 0.78). Preliminary interim data.

4. Discussion

This study examined two functional promoter polymorphisms of the principal early cytokines of post-traumatic neuroinflammation, IL-6 -174 G/C and TNF-α -308 G/A, and linked them to a routinely measurable inflammatory biomarker, CRP, and to the clinically important endpoint of infectious-inflammatory complications after TBI. The conceptual strength of pairing these two variants is that they converge on a shared downstream read-out: both cytokines promote hepatic CRP synthesis and a systemic inflammatory state that predisposes to nosocomial infection and secondary deterioration.

The analytical framework is consistent with previous candidate-gene work in TBI. The high-expression IL-6 -174 G allele has been associated with short-term survival differences after severe injury [8], and the TNF-α -308 genotype has been related to 6-month Glasgow Outcome Scale scores in independent cohorts [9]. At the same time, the literature is not uniform: several studies have found no significant association between IL-6 promoter variants and outcome [10], reflecting differences in cohort size, injury-severity mix, ethnicity-dependent allele frequencies and outcome definitions. Interpreting the present data within this mixed evidence base, rather than in isolation, is therefore essential.

Mechanistically, CRP provides a coherent integrator of the two genetic signals. Because IL-6 is the dominant inducer of hepatic CRP and TNF-α amplifies the same acute-phase programme, a genotype that increases cytokine output is expected to manifest as higher peak CRP and, in turn, a greater burden of infectious-inflammatory complications. This logic supports the use of CRP not merely as a severity marker but as a mechanistic link between inherited variation and clinical risk, and it justifies the analytic sequence used here, from genotype to CRP to complication.

At the molecular level the two cytokines act through partly distinct but reinforcing routes. IL-6 signals through both the membrane-bound receptor (classic signalling) and the soluble receptor (trans-signalling), the latter extending its action to cells that lack the membrane receptor and contributing to the inflammatory state of injured brain tissue; its

net effect after TBI is context-dependent, with both deleterious and reparative components reported [4]. TNF-α contributes to blood-brain barrier breakdown, microvascular dysfunction and apoptotic signalling, and amplifies the production of other inflammatory mediators. Because both pathways feed the hepatic acute-phase response, CRP reflects their combined output more completely than either cytokine measured alone, which is a further rationale for using it as the integrating biomarker in this study [11].

Clinically, if confirmed in adequately powered samples, a simple two-locus genotype combined with the early CRP trajectory could contribute to risk stratification, identifying patients in whom heightened surveillance for pneumonia, meningitis or ventriculitis and sepsis, and more conservative thresholds for infection work-up, may be warranted. Such stratification would be most valuable in resource-constrained neurocritical-care settings, where targeting intensive monitoring to higher-risk patients has practical value.

Strengths of the present approach include its prospective design with a pre-defined acute sampling schedule, the use of serial rather than single CRP measurements, standardised outcome assessment with the GOS-E at two time points, and the deliberate pairing of two functionally convergent loci with a shared biomarker rather than the analysis of isolated single-nucleotide polymorphisms. The study also addresses an ethnically distinct and under-represented population, for which allele-frequency and association data in TBI are scarce; such data are needed before genotype-based risk tools can be applied across diverse settings.

Limitations

Several limitations must be emphasised. First, the sample size required by the a priori power calculation (of the order of 114 to 219 participants per group to detect an OR of 2.0 at 80% power after multiple-testing correction) is substantial; until recruitment reaches this target the quantitative estimates should be read as preliminary and hypothesis-generating. Second, the single-centre design limits generalisability, and allele frequencies of both variants differ across populations, so external validation is necessary. Third, CRP is sensitive but non-specific and is influenced by extracranial injury and intercurrent infection; serial sampling and adjustment mitigate but do not eliminate this. Fourth, only two loci were examined here; the broader genetic architecture, including antioxidant, endothelial and folate-pathway genes and the rare APOE rs769452 variant, is addressed in companion analyses, and gene-gene (haplotype) interactions were not modelled. Finally, the observational design precludes causal inference.

Future work should prioritise completion of recruitment to the pre-specified target, multicentre replication, and joint modelling of the inflammatory loci with the other functional gene clusters under study, so that additive and interactive genetic contributions to post-traumatic complications can be assessed within a single predictive framework.

5. Conclusion

Promoter polymorphisms of IL-6 (-174 G/C, rs1800795) and TNF-α (-308 G/A, rs1800629), interpreted together with CRP as a shared inflammatory read-out, represent biologically plausible molecular markers for the risk of infectious-inflammatory complications after traumatic brain injury. The present work establishes the methodological framework and the expected directions of association; adequately powered, multicentre confirmation is required before clinical application.

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